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Gut microbiota and ovarian diseases: a new therapeutic perspective

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Abstract
The gut microbiota is a complex community of microorganisms that inhabit the human gastrointestinal tract, helping to maintain the ecological balance of the body's internal and external environments. Disruptions in the composition and diversity of gut microbiota, as well as changes in their metabolic functions, can link to the development and severity of conditions such as premature ovarian insufficiency, polycystic ovary syndrome, and ovarian tumors. This article thoroughly reviews recent research on the connection between gut microbiota and ovarian diseases, providing fresh perspectives on their prevention, pathogenesis, and treatment.

Keywords Gut microbiota, Premature ovarian insufficiency, Polycystic ovary syndrome, Ovarian tumors

Introduction

The ovaries secret sex hormones that maintain the normal function of many female organs, thereby playing a crucial role in women's reproductive and endocrine functions [1–2]. Much research has been done on ovarian inflammation [3–4], polycystic ovary syndrome [5, 6], and ovarian tumors [7, 8], all of which are prevalent in women. The human gut microbiome is a diverse and intricate community of microorganisms that inhabit the gastrointestinal tract, and these include bacteria, viruses, and fungi [9, 10]. This community is composed of approximately 10^{13} to 10^{14} microorganisms, including over 1,000 species and more than 7,000 strains [11].

The gut microbiota is essential in shaping and developing the immune system [5, 12], in addition to preventing infection [13], aiding nutrient supply, and maintaining brain and nervous system function in the host [14]. Imbalances in the composition [15] and diversity of the gut microbiota [16], along with altered metabolic function [17], can cause inflammation and increased gut permeability, both of which result in disease [18]. The gut microbiota affects brain function via the gut-brain axis [19]. It activates neurons through the vagus nerve, endocrine signaling, and immune pathways [20–22]. Significant changes in microbiota were observed in various ovarian diseases. This highlighted a strong association between the gut microbiota and ovarian disease [23]. Results from animal studies have indicated a potential causal relationship between the gut microbiota and ovarian diseases, possibly through regulatory pathways [24–27], immune responses, or pathogenic mechanisms [28, 29]. However, there is no clarity as to

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whether the alterations in the gut microbiota are a cause, consequence, or mere coincidence in the development of these diseases. Therefore, more research is necessary to confirm the potential benefits of targeting the gut microbiota in disease treatment. This paper reviews the latest advancements in research on gut microbiota and ovarian diseases, to offer new perspectives for preventing and treating these conditions. The findings from this review also unleash more information regarding the pathogenesis of ovarian diseases.

Methodology

Two doctoral researchers systematically reviewed studies published in the past ten years on the relationship between gut microbiota and ovarian diseases, prioritizing those with human clinical data, followed by well-designed animal experiments. The selection criteria focused on studies exploring the associations between gut microbiota composition and common ovarian diseases, such as polycystic ovary syndrome (PCOS), premature ovarian insufficiency (POI), endometriosis, and ovarian cancer. Studies were excluded if they: (1) investigated gut microbiota in non-ovarian diseases (e.g., diabetes, cardiovascular disorders); or (2) employed concurrent therapies known to interact with gut microbiota (e.g., antibiotics, probiotics, or fecal microbiota transplantation) without controlling for their confounding effects.

Based on the collected evidence, we analyzed the role of gut microbiota dysbiosis in ovarian disease pathogenesis, particularly its impact on inflammatory and metabolic pathways. This review also highlights the potential of gut microbiota modulation as an adjunctive therapeutic strategy for ovarian diseases, providing new perspectives on its clinical applications in reproductive health.

Gut microbiota and premature ovarian insufficiency

Premature ovarian insufficiency (POI) is characterized by ovarian hypofunction or decline in women who are under the age of 40. This is mainly evidenced by abnormal menstruation traits, which include the following: amenorrhea; scanty or frequent periods; elevated follicle-stimulating hormone (FSH) (> 25 IU/L) and luteinizing hormone (LH) concentrations; and low estradiol (E_2) levels [30]. POI is caused by various factors such as genetics, immunology, medicine, infection, and the environment [31]. It is important to note that POI may have a significant impact on the physical and mental health of women [32].

POI has become one of the biggest reproductive health threats to women who belong to the childbearing age groups. Findings from animal experiments confirmed the connection between POI and disturbances in gut microbiota balances. The lycium barbarum polysaccharide (LBP) has anti-aging and reproductive protection functions. Zheng H et al. investigated the protective effects of LBP regarding the development of POI in mice. The researchers further explored the underlying mechanisms through 16 S rRNA sequencing. In this study by Zheng and colleagues, female C57BL/6J mice treated with D-galactose served as models for assessing LBP's ability to reverse degenerative ovarian function. Improvements in POI were evaluated based on the estrous cycle, ovarian reserve, sex hormone levels in the serum, and fertility tests. Additionally, 16 S rRNA gene sequencing was employed to examine the impact of LBP on the gut microbiota and fecal metabolic profiles of POI mice. The results demonstrated that LBP administration significantly increased the number of follicles at various developmental stages in the POI mice. Logically, the total number of follicles also rose. Additionally, LBP effectively lowered the levels of serum FSH and LH, corrected the discrepancies in the estrous cycle, and raised the number of offspring in POI mice. The results from 16 S rRNA sequencing revealed that LBP positively influenced the composition and structure of the gut microbiota in POI mice. Pearson's correlation analysis further indicated that the regulatory effects of LBP on gut microbiota metabolites were closely associated with the presence of Faecalis, Bilophila, and anaerobic bacteria [25].

Geng Z et al. discovered that electroacupuncture (EA), a traditional Chinese medicine therapy, can regulate intestinal microecology and protect the intestinal barrier. This adjusts the abundance of intestinal microbiota, thereby improving reproductive function. In the study, 36 female C57BL/6 mice were randomly assigned to three groups as follows: the wild-type group (WT, $n = 12$); the POI group (POI, $n = 12$); and the EA treatment group (EA, $n = 12$). The EA group received electroacupuncture at the Guanyuan (CV4), bilateral Zusanli (ST36), and Sanyinjiao (SP6) points every two days, for four consecutive weeks. Sterile acupuncture needles were inserted into CV4, ST36, and SP6 at depths that ranged from 2 to 5 mm, as the mice were stimulated using a continuous wave with a frequency of 1–3 Hz and an intensity of 0.1-1 mA. HPLC-MS/MS assay results indicated that levels of estrone (E_1), estradiol (E_2), estriol (E_3), and 21-deoxycortisol (21D) were significantly reduced in the POI group compared to the WT group. The results indicated that the levels of these hormones were, to some extent, restored after EA treatment. EA treatment improved hormonal levels in POI mice. Stool samples from all three groups were simultaneously sequenced four weeks after EA treatment. The findings revealed a significant reduction in the overall abundance of gut microbiota in the EA group. However, an increase in the diversity and distribution of bacterial species was noted in the same group. Based on phyla microbial

composition, Firmicutes and Bacteroidetes accumulated to less than 80% of the entire microbial community in the WT and EA groups, whereas in the POI group, they accounted for more than 80%. At the class level, Clostridium and Bacteroides comprised less than 60% of the microbial community in the WT and EA groups. In the POI group, these bacteria accounted for over 70%. At the phylum level, the relative abundance of Actinobacteria was significantly reduced in the POI group compared to the WT group. Following EA treatment, the relative abundance of Tenericutes significantly decreased, while that for Actinobacteria increased compared to the POI group. At the genus level, the relative abundance of Alistipes was significantly higher in the POI group than in the WT group. However, after EA treatment, the relative abundance of Alistipes and Pantoea significantly reduced compared to the findings from the POI group [26].

The Shin SY study found that POI induced dysregulation of intestinal bacterial flora and POI in guinea pigs through cecal operation laparotomy. One group of guinea pigs was orally pretreated with probiotics within seven days before surgery-induced POI. Fecal particles were collected, followed by DNA extraction before surgery (baseline group), and then 1, 3, and 5 days after the surgery. The results revealed significant differences in bacterial composition between the baseline and POI groups. The Bifidobacteria and Lactobacillus were more abundant in the baseline group than in the POI group. Bacteroides and Cyanobacteria were more abundant than those in the baseline than the POI group. In the probiotic group, the abundance of Bifidobacterium and Bifidobacterium longum species significantly decreased after POI modeling [27].

A comparative study between 18 healthy women and 35 patients with POI revealed significant differences in gut microbiota [33]. The healthy women had a higher abundance of gut bacteria from the Thick-Walled Bacteria, Herpes maculans, and Enterococcus faecalis phyla were observed in the healthy women, Mycobacterium phylum, Butyric acid bacteria, Doriaceae, and Lactobacillus genus where more abundant in POI patients. These findings demonstrate the clear distinction between the gut microbiota composition of healthy women and those with POI. The study found a negative correlation between E2 levels and the relative proportions of Mycobacterium phylum and Mycobacterium phylum/thick-walled bacteria ratio. On the other hand, a positive correlation was noted between E2 levels and the relative proportions of thick-walled bacteria and Escherichia coli. The study found a significant and positive correlation between the relative proportions of Mycobacterium avium and FSH levels. Additionally, there was a positive correlation between the FSH/LH ratio and the relative proportions of both M. avium and E. faecalis. The FSH/LH ratio negatively correlated with the relative proportions of Firmicutes and E. faecalis. These findings highlight a strong relationship between the changes in the gut microbiota of POI patients and the variations in hormonal levels in their serum [34].

A dangerous industrial material called 4-vinyl cyclohexene dioxide (VCD) is widely used in the production of fragrances, rubber tires, and plasticizers. VCD can damage the female reproductive system. Cao et al. observed differences in the gut microbiota of the VCD-induced POI mouse model compared to healthy mice. A total of 33 genera were more abundant in the POI group versus the 15 genera in the control group. The gut microbiota of mice induced by VCD was extracted and added to the nematode medium, resulting in a significant change in nematode colonization. These findings provide strong evidence for the association between E2 levels and gut microbiota, as well as between POI and gut microbiota [35].

Lin et al. demonstrated that Fisetin can alleviate ovarian damage and increase the number of normal follicles in POI mice. This is achieved by regulating Ackermannia and Lactobacillus bacterial counts, reducing $CCR9^{+}$/ $CXCR3^{+}$/ $CD4^{+}$ T-lymphocyte counts, as well as IL-12 secretion in mice, controlling the ovarian microenvironment, and alleviating inflammation. These findings highlight the potential therapeutic use of Fisetin in treating POI. Molecular analysis results demonstrate that carbohydrate and nucleotide metabolism increased in the gut microbiota of the mice in the Fisetin group. On the contrary, lipid and amino acid metabolism had decreased. Homologous protein cluster of orthologous groups of proteins (COG) analysis revealed a significant rise in the abundance of proteins associated with transcription, translation, ribosome structure, and synthesis, as well as carbohydrate metabolism, and nucleotide transport in gut microbes. These proteins promote the activation of membrane transport, in addition to aiding cell motility and translation in mice [36].

Clinical and laboratory studies further revealed an association between gut microbiota and POI (Figs. 1 and 2). This indicates that modulating the gut microbiota could be a potential solution for managing POI and improving clinical symptoms in patients. Recent scientific research has significantly advanced our understanding regarding the role of gut microbiota in primary POI. However, there is a limited number of articles that report the interaction between the microbiome and progression of primary POI, the possible mechanism of action, as well as the improvement of primary POI due to altered gut microbiota (flora transplantation). It remains unclear whether changes in the gut microbiome are a cause or a consequence of primary POI. The precise timing at which the gut microbiome influences ovarian aging is

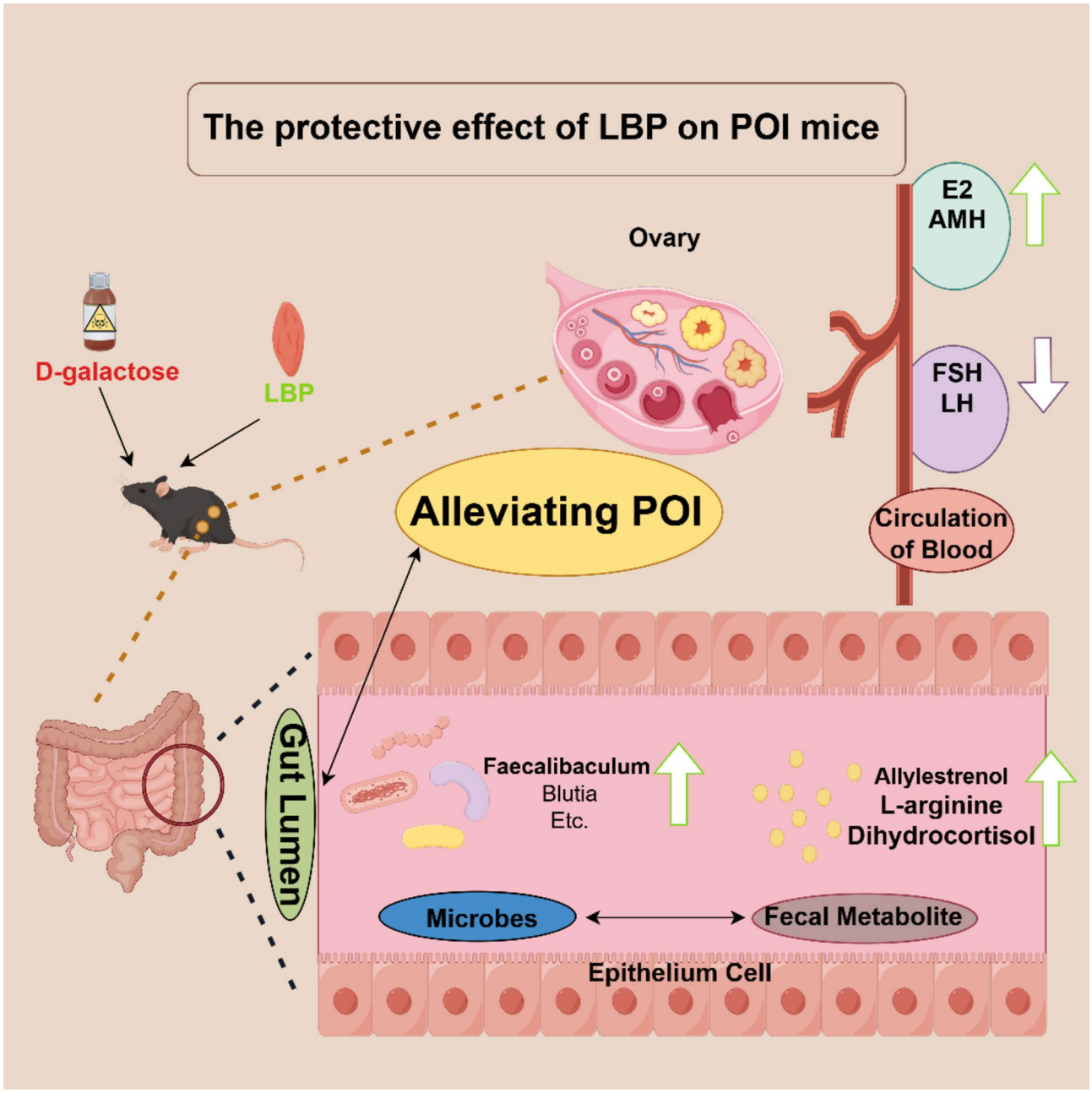

Fig. 1 LBP significantly increased the total number of follicles and the number of follicles in POI mice at different developmental stages. In addition, LBP effectively reduced serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), normalized estrous cycle disturbances, and increased the number of offspring in POI mice. By Figdraw

not yet defined. The specific mechanisms underlying this relationship still require further investigation. Existing scientific literature links only a few groups of bacteria groups to the development and progression of POI. Moreover, the available evidence is relatively fragmented. The reported effects may point to multiple mechanisms. Moreover, the roles and molecular pathways of specific bacterial strains or their metabolites are not fully understood, as far as follicular development is concerned.

Hormone replacement therapy (HRT) is currently the primary treatment recommended for managing symptoms and preventing disease in women with POI. HRT can significantly reverse changes in serum metabolites as well as E_2 and progesterone levels associated with POI. However, HRT has potential side effects and contraindications. Consequently, research on the drug interventions that improve intestinal microbial imbalances and promote a healthier gut environment is still underway, in a bid to alleviate primary POI. Current scientific

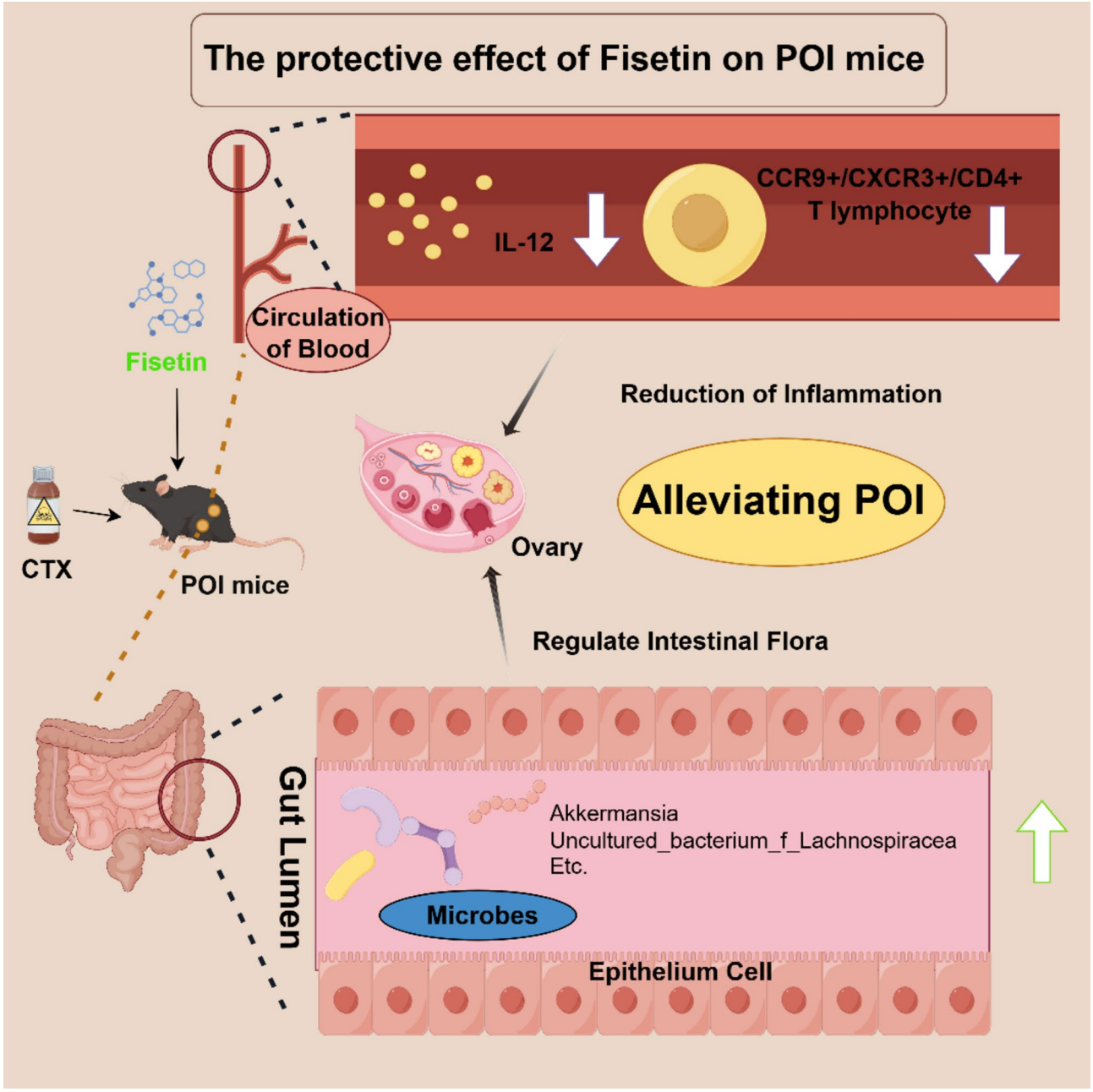

Fig. 2 Fisetin alleviate ovarian damage and increase the number of normal follicles in POI mice by regulating Ackermannia and Lactobacillus bacterial counts, reduction of CCR9+/CXCR3+/CD4 + T lymphocyte counts and IL-12 secretion in mice, regulation of the ovarian microenvironment, and reduction of inflammation. By Figdraw

literature does not offer direct conclusions regarding these measures. Most relevant studies have been conducted in animal models, which may not directly translate to successful application in humans. Thus, future research, including simple correlation analyses and large-scale cohort studies, should focus on investigating potential causal relationships and mechanisms that validate the beneficial effects of these interventions on primary POI.

Gut microbiota and polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is a complex, polygenic disorder that is characterized by hyperandrogenism, ovulatory dysfunction, and the presence of polycystic ovarian morphology (PCOM) [37]. Its incidence has gradually increased in recent years, reaching up to 6-10% [38].Several factors have been linked to the hormonal and metabolic imbalances that may cause the development of PCOS [39]. PCOS patients exhibit various endocrine and metabolic abnormalities, such as

elevated serum LH and androgen levels, reduced FSH concentrations, insulin resistance (IR), obesity, and dyslipidemia [40]. Furthermore, these patients are more vulnerable to hypertension and cardiovascular disease. PCOS has a multifaceted etiology, which includes genetic and epigenetic factors that affect various clinical phenotypes. These phenotypes are characterized by specific signs and symptoms, such as menstrual dysfunction, subfertility, acne, hirsutism, and obesity, which significantly impact several domains related to the quality of life, including sexuality [41].

To diagnose PCOS according to the Rotterdam 2003 criteria, three conditions must be met as follows: (1) irregular or absent ovulation; (2) clinical or biochemical signs of hyperandrogenism; and (3) the presence of PCOM on ultrasound [42]. PCOM is characterized by an ovarian volume that is greater than 10 ml and at least 12 follicles of 2–9 mm in diameter, visible in one ovary. It is crucial to exclude other hyperandrogenic conditions, such as congenital adrenal hyperplasia, Cushing's syndrome, and ovarian or adrenal tumors when diagnosing PCOS. PCOS patients experience psychological issues such as depression and anxiety, in addition to discrepancies in fertility [43, 44].

The relationship between PCOS and gut microbiota has been extensively studied. Significant differences in gut microbiota have been consistently reported between patients with different types of PCOS and healthy populations. Variations in alpha and beta diversity are among the noted differences. Alpha diversity measures ecosystem health, thereby reflecting the abundance and diversity of species within a community. On the other hand, beta diversity significantly affects bowel function, insulin levels, glucose tolerance, and androgen levels [45], all of which can worsen the symptoms of PCOS [46–47]. Extensive research on PCOS and gut microbiota composition has revealed a strong correlation between the disease and the abundance of specific gut microbiota at various classification levels, including phylum, family, and genus.

The gut microbiota is composed mainly of thick-walled bacteria and Mycobacterium phyla, which account for 90% of its composition [48]. The Actinobacteria, Aspergillus, and Clostridium phyla are also present. The thick-walled strain mainly produces butyrate, while the anaphylatoxigenic strain produces acetate. In the study by Torres PJ, 163 premenopausal women were recruited from Poznan University of Medical Sciences. Fecal microbial diversity profiles were analyzed using 16 S ribosomal RNA gene sequencing in three groups as follows: healthy women ($n = 48$); women with PCOS ($n = 42$); and women diagnosed with PCOS according to the Rotterdam criteria ($n = 73$). Women with PCOS exhibited lower alpha diversity compared to healthy women. The alpha diversity in women with PCOM fell between the two other groups. Regression analysis revealed that hyperandrogenemia, total testosterone, and hirsutism negatively correlated with alpha diversity. Permutation multivariate analysis of UniFrac distance variance indicated that hyperandrogenemia was also associated with beta diversity. Random Forest analysis identified specific bacteria that distinguished healthy women from those with PCOS. Compared to the control group and PCOM patients, higher serum levels of total and free testosterone were noted in women with PCOS, along with increased hirsutism and reduced menstrual frequency. Additionally, LH levels in the serum of women with PCOS were elevated and the LH/FSH ratio increased. However, no significant changes in serum FSH levels were detected [45].

Zhou L et al. carried out a study that included 60 women with PCOS, aged between 16 and 35 years. The researchers divided the participants into 30 obese (OG) and 30 non-obese (NG) PCOS patients. A total of 30 healthy women (NC) and 11 healthy but obese women (OC) were included as controls. The study aimed to explore the characteristic gut microbiota and metabolic function in obese and non-obese PCOS patients. Blood and non-menstrual stool samples were collected and analyzed from all participants. The results showed that the NG and OG patients had significantly higher hirsutism scores, LH/FSH ratios, and serum testosterone levels compared to the control group. High-throughput 16 S rRNA gene sequencing revealed alterations in the abundance and diversity of the gut microbiota in PCOS patients. Linear discriminant analysis identified Lactococcus as prevalent in the NG gut microbiota, while Coprococcus was prominent in that of the OG. The study indicated that changes in serum sex hormones and insulin levels were closely associated with gut microbiota alterations in both NG and OG PCOS patients [39].

Jamilian M. et al. assessed the effects of probiotics and selenium supplementation on hormonal response biomarkers, inflammation, and oxidative stress in women with PCOS. Sixty women with PCOS were randomly assigned to two groups. One group received 8×10^9 CFU/day of Tienyi bacteria, which included Lactobacillus acidophilus, Lactobacillus reuteri, Lactobacillus fermentans, and Bifidobacterium bifidum, along with 200 μg/day of selenium ($n = 30$). The other group received a placebo ($n = 30$). The intervention lasted for 12 weeks. The study found that co-administrating probiotics and selenium reduced total testosterone levels in women with PCOS. The findings also showed that supplementation with Biostime for 12 weeks lowered the sex hormone-binding globulin levels in women with PCOS. In addition, 12-week supplementation with probiotics significantly improved hirsutism, total testosterone, and sex hormone-binding globulin values in women with PCOS. It

was hypothesized that the mechanism by which probiotics improve hormonal status is associated with changes in the intestinal microbiota, along with enhanced digestion and absorption of dietary nutrients. The potential effects of selenium supplementation on hormonal parameters can be explained by its ability to reduce oxidative stress and increase enzymatic antioxidant activity. The co-supplementation of probiotics and selenium in PCOS patients significantly reduced the levels of C-reactive protein and malondialdehyde. However, it's important to note that total glutathione concentrations remained unchanged, and this enhanced the antioxidant status in the patients. Jamilian M et al. suggest that the combination of probiotics and selenium supplementation could be considered a new approach for treating PCOS [47].

Studies have indicated that women with PCOS tend to have lower levels of gut microbiota that produce short-chain fatty acids (SCFAs). Supplementation with SCFAs, such as butyrate, has been shown to prevent insulin resistance and obesity by enhancing energy expenditure in mice fed on a high-fat diet [49, 50]. This suggests that SCFAs are vital for maintaining a healthy gut microbiome in women with PCOS. SCFAs help to sustain a balanced gut pH, support the growth of beneficial bacteria like Lactobacillus and Bifidobacterium, as well as inhibit the proliferation of opportunistic pathogens such as Clostridium and E. coli. SCFAs also play a crucial role in protecting the intestinal barrier function. They stimulate the regeneration of epithelial cells and the production of mucus and antimicrobial peptides, thereby inhibiting the translocation of toxins and bacteria into the bloodstream. This helps to prevent cancer, obesity, chronic inflammation, and metabolic syndrome [51, 52]. Kelley et al. demonstrated the changes in gut microbiota at the phylum level, using a letrozole-induced PCOS mouse model [53].The study reveals a significant reduction in the total number of microbial species in the gut. The phylogenetic richness was also compromised [54]. These changes were primarily attributed to a decrease in the Mycobacterium phylum and an increase in the thick-walled Bacteroides phylum [55].

Li R et al. demonstrated that the Astragalus polysaccharide (APS) ameliorated PCOS in mice, by addressing serum metabolic disorders and enhancing microbiome diversity. In the study, three-week-old BALB/C female mice were randomly assigned to three groups, each of which had 10 mice. The groups were as follows: oil + PBS group; dehydroepiandrosterone (DHEA) + PBS group; DHEA + APS group. The researchers assessed changes in the estrous cycle, ovarian tissue morphology, serum hormone levels, blood glucose, and blood lipid profiles. The gut microbiome was also analyzed through sequencing, while the correlation between serum metabolic markers and gut microbiota was examined using Spearman correlation analysis.

The results indicated that APS treatment improved insulin resistance and dyslipidemia in PCOS mice. The results from 16 S rDNA sequencing revealed significant differences in the composition and diversity of gut microbiota among the different groups. In the oil + PBS group, Firmicutes, Lachnospiraceae, Bacilli, and Lactobacillaceae were more abundant. The DHEA + PBS group showed an increased enrichment of Bacteroidota and Muribaculaceae, while higher levels of Rikenellaceae, Odoribacter, and Marinifilaceae were observed in the DHEA + APS group. Spearman correlation analysis found strong associations between gut bacteria and blood glucose, lipids, steroid hormones, and oxidative stress markers in PCOS mice. APS improved PCOS symptoms by correcting serum metabolic disorders and increasing microbiome diversity, potentially offering new insights that aid better understanding regarding the pathogenesis of PCOS, thereby enhancing its treatment [50].

He Y et al. found that butylated starch (BS) could alleviate ovarian morphological abnormalities, metabolic disorders, and sex hormone imbalances in rats that were treated with letrozole. Resistant starch may improve PCOS symptoms through the help of SCFAs, which play a crucial role in the gut microbiome-dependent treatment of PCOS. When corn starch is acylated with specific SCFAs, it releases acetate, propionate, and butyrate into the cecum and colon. Additionally, BS activates the G-protein-coupled receptor GPR41, thereby causing peptide tyrosine-tyrosine to be secreted into the serum. This further influences the disease phenotype. The study also found that BS had a more pronounced effect on fecal microbiota than on cecal microbiota the enrichment of butyrate-producing microorganisms in the stool after BS treatment potentially contributed to further alleviation of PCOS symptoms [52].

Huang J et al. found that macrophage pyroptosis, which is induced by imbalances in the gut microbiota and exacerbated by IFN-γ, plays a critical role in the pathogenesis of PCOS. This study highlighted that LPS-induced macrophage pyroptosis, which is linked to the dysregulation of gut microbiota, significantly contributes to the development of PCOS. The research demonstrated that macrophage pyroptosis promotes apoptosis and disrupts estrogen production in granulosa cells. Elevated levels of IFN-γ in the serum and ovaries of PCOS mice further intensified macrophage pyroptosis, worsening its impact on granulosa cells, and thereby aggravating the progression of PCOS [54].

Zhang H et al. reported that omega-3 polyunsaturated fatty acids (PUFAs) could improve androgen-induced intestinal microbiota dysregulation, thereby improving ovarian dysfunction. PCOS was induced in female mice

by administering DHEA, followed by treatment with omega-3 PUFAs. Using 16 S ribosomal DNA (rDNA) amplicon sequencing, fecal microbiota transplantation (FMT), and antibiotics the study assessed the role of the microbiota in regulating ovarian function and insulin resistance (IR) by omega-3 PUFAs. Oral supplementation with omega-3 PUFAs improved the PCOS phenotype. The findings from 16 S rDNA sequencing revealed that treatment with omega-3 PUFAs increased the abundance of beneficial gut bacteria, thereby mitigating DHEA-induced dysbiosis. Antibiotic treatment and FMT experiments indicated that omega-3 PUFAs might have direct effects on the ovaries. For example, they might inhibit inflammatory cytokines such as IL-1β, TNF-α, and IL-18. Thus, considering that omega-3 supplementation can modulate the gut microbiome and alleviate ovarian dysfunction, it is a promising approach for treating PCOS [55].

Qiao Jie et al. found a significant increase in Bacteroides vulgatus in the gut microbiota of individuals with PCOS. The researchers also observed lower levels of glycodeoxycholic acid and tauroursodeoxycholic acid in the participants. Transplanting fecal microbiota from women with PCOS to recipient mice colonized with Bacteroides vulgatus resulted in several adverse health outcomes, including increased ovarian dysfunction, insulin resistance, altered bile acid metabolism, reduced interleukin-22 (IL-22) secretion, and infertility. The study also highlighted that glycodeoxycholic acid stimulates group 3 innate lymphoid cells to produce IL-22 via GATA binding protein 3. It was also revealed that IL-22 helps ameliorate the PCOS phenotype. Furthermore, reduced IL-22 levels have been observed in PCOS patients. These findings suggest that modifying the gut microbiota, altering bile acid metabolism, and/or increasing IL-22 levels could be potential strategies for treating PCOS, further demonstrating the potential that lies in targeted interventions for addressing the condition [56].

Xue J et al. investigated the effects of inulin and metformin on PCOS, mainly focusing on anti-inflammatory properties and impacts on the gut microbiota. Mice were divided into four groups as follows: control (CON); model (MOD); inulin (INU); and metformin (MET). The INU, MET, and MOD groups were given 6 mg of DHEA and fed on a 60% high-fat diet per 100 g body weight to induce a PCOS model. The treatment lasted 21 days. The results showed that both inulin and metformin significantly reduced body weight (BW) and testosterone (T) levels, while estradiol (E2) levels increased in all these groups. The ovarian tissues were subjected to HE staining and the findings indicated that inulin and metformin improved PCOS morphology.

Inflammatory markers such as TNF-α, IL-6, and IL-17 A, were reduced in the plasma and ovaries of the INU and MET groups. Metagenomic analysis of fecal samples revealed that the levels of Bifidobacteria increased in the INU group, while those for Proteobacteria, Helicobacter pylori, and Parataxella decreased in the MOD group. Helicobacter pylori levels were also reduced in the MET group. The probiotic Bifidobacterium has been shown to inhibit the synthesis of pro-inflammatory cytokines. Interestingly, inulin increased the abundance of Bifidobacterium, thus improving the symptoms of PCOS. Plasma LPS levels were significantly lower in the INU and MET groups, suggesting that inulin and metformin may reduce intestinal permeability and limit LPS translocation from the gut to the liver and bloodstream. The reduced systemic inflammation may suggest that inulin and metformin as potential alternatives for the clinical treatment of PCOS [57].

Wang et al. highlighted the significant influence of gut microbiota on the progression of PCOS by regulating hormone secretion, gut-brain mediators, cytokines, and metabolite production [46]. Additionally, a human study demonstrated that colonization with a Bifidobacterium lactis strain effectively altered the gut microbiota of PCOS patients and restored their sex hormone levels [58]. However, further research is needed to determine the effects of specific probiotic strains on the gut microbiota, as well as their roles in PCOS-related microbial taxa [59].

Zhou et al. showed that patients with polycystic ovary syndrome have lower abundance and diversity of gut microbiota compared to healthy women [60, 61]. Furthermore, specific bacterial genera can impact the host gut environment through differential gut enrichment and metabolism [61], potentially contributing to the development of PCOS in obese women with PCOS. The study found that PCOS patients have lower abundance and diversity compared to the non-PCOS population. The obese polycystic ovary syndrome group showed significantly lower ratios of thick-walled Bacteroides / Mycobacterium phylum and significantly increased levels of Clostridium colorless, Clostridium spp, and Faecococcus spp, which are characteristic genera of obese PCOS patients. Fecal metabolites closely related to the gut microbiota were identified as characteristic metabolites of obese PCOS. These metabolites showed significant correlation with serum sex hormone levels, including elevated LH, decreased FSH, and elevated serum androgen levels, as well as gut microbiota abundance. The gut microbiota contributes to the development of polycystic ovary syndrome by promoting host insulin resistance, low-grade inflammation, and hyperandrogenemia through molecular interactions with the host [62]. Zhou et al. showed that patients with PCOS have a lower abundance and diversity of gut microbiota compared to healthy women [60, 61]. Furthermore, specific bacterial

genera can impact the host gut environment through differential gut enrichment and metabolism [61], potentially contributing to the development of PCOS in obese women. The obese PCOS group showed significantly lower ratios of thick-walled Bacteroides/Mycobacterium phylum and significantly increased levels of Clostridium colorless, Clostridium spp, and Faecococcus spp, which are the characteristic genera of obese PCOS patients. Fecal metabolites that are closely related to the gut microbiota were identified as characteristic metabolites of obese PCOS. Significant correlation was noted between these metabolites and the serum sex hormone levels, including reduced FSH, as well as elevated LH and androgen levels. The metabolites also correlated with gut microbiota abundance. The development of PCOS is influenced by the gut microbiota, which exacerbates insulin resistance, low-grade inflammation, and elevated androgen levels through molecular interactions with the host [62].

LPS produced by the gut microbiota exhibit endotoxic effects, which contribute to its crucial role in the early development of inflammatory and metabolic diseases [63]. LPS enters the bloodstream and attaches to the CD14 toll-like receptor complex (TLR-4), located on the surface of innate immune cells [64]. This activates downstream signaling pathways that interfere with the function of insulin receptors, a state that increases insulin levels in the serum [65, 66]. Endotoxin-induced macrophage activation leads to elevated serum levels of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [67, 68].Research has shown that directly introducing LPS into the bloodstream of both mice and humans elevates fasting blood glucose and insulin levels [69]. Impaired gut barrier function allows endotoxins produced by the gut microbiota to enter the bloodstream, leading to chronic inflammation of the ovaries and IR [70]. This, in turn, strongly contributes to the development of PCOS. In their study on a rat model of PCOS induced by various factors, Chu Weiwei et al. found that rats given continuous light after DHEA injection exhibited significant differences in microbiota structure compared to both DHEA alone and control rats. These results demonstrate the clear impact of continuous light on the microbiota structure in rats with PCOS induced by DHEA injection. The gut microbiota of DHEA + light rats showed significant differences, with Staphylococcus and Woolly Snail being significantly enriched in the intestine, while Heterophile and Bacillus koalasii levels were significantly reduced. Functional predictions strongly suggest that these differences are associated with several possible gluconeogenic pathways in PCOS [71]. Disturbances in the gut microbiota promote the production of inflammatory factors such as TNF-α and IL-6, which stimulate upregulation of the expression of the steroid hormone synthase CYP17. This induces hyperandrogenemia and exacerbates the development of PCOS [72, 73].

Clinical and laboratory research has revealed a link between gut microbiota and PCOS (Fig. 3). Recent scientific studies have advanced the current level of understanding regarding the gut microbiome's role in PCOS. These studies identified alterations such as reduced abundance and diversity, in the gut microbiome among PCOS patients. Specific bacterial genera have been found to impact the host's intestinal environment through variations in enrichment and metabolism, potentially contributing to PCOS, particularly in obese women. Additionally, research indicates that women with PCOS often have lower levels of certain SCFA-producing gut microbiota. SCFAs are crucial for maintaining the intestinal functional barrier. They also help to maintain a healthy gut pH while promoting the growth of beneficial bacteria such as Lactobacillus and Bifidobacterium. Additionally, SCFAs inhibit the growth of conditioned pathogens such as Clostridium or E. coli. Some therapeutic methods or chemical components have been applied in animal models and human bodies. The structure of gut microbiota is regulated through direct supplementation of probiotics, biostime composed of probiotics, or complementary chemical components. The metabolic function of the intestine is enhanced by fostering the growth of beneficial bacteria and suppressing opportunistic bacteria. This ultimately helps to regulate ovarian endocrine function. However, current scientific literature does not offer direct evidence to support these measures. Thus, future research should progress from basic correlation analyses to large-scale cohort studies, concentrating on potential causes and action mechanisms, to confirm the beneficial effects of these interventions in treating PCOS.

Gut microbiota and ovarian cancer

Ovarian malignancy is the third most common gynecological cancer [74], after cervical and endometrial tumors [75, 76]. However, the mortality rate associated with ovarian malignancy is at the top of female genital tract cancers. It's also important to note that the recurrence rate of this malignancy after treatment is high, as it continues to increase annually [77, 78]. Patients often present clinically with significant lower abdominal discomfort, bloating, and loss of appetite, with gastrointestinal symptoms prominent in the overall course of treatment [79, 80].

Humans host a diverse range of microorganisms across various organs, including the gut, respiratory tract, and reproductive tract. These microorganisms are crucial for maintaining health. Microbial diversity imbalances in the reproductive and gut tracts can contribute to the development and progression of diseases such as ovarian cancer. The microbiome may play an incidental or associative

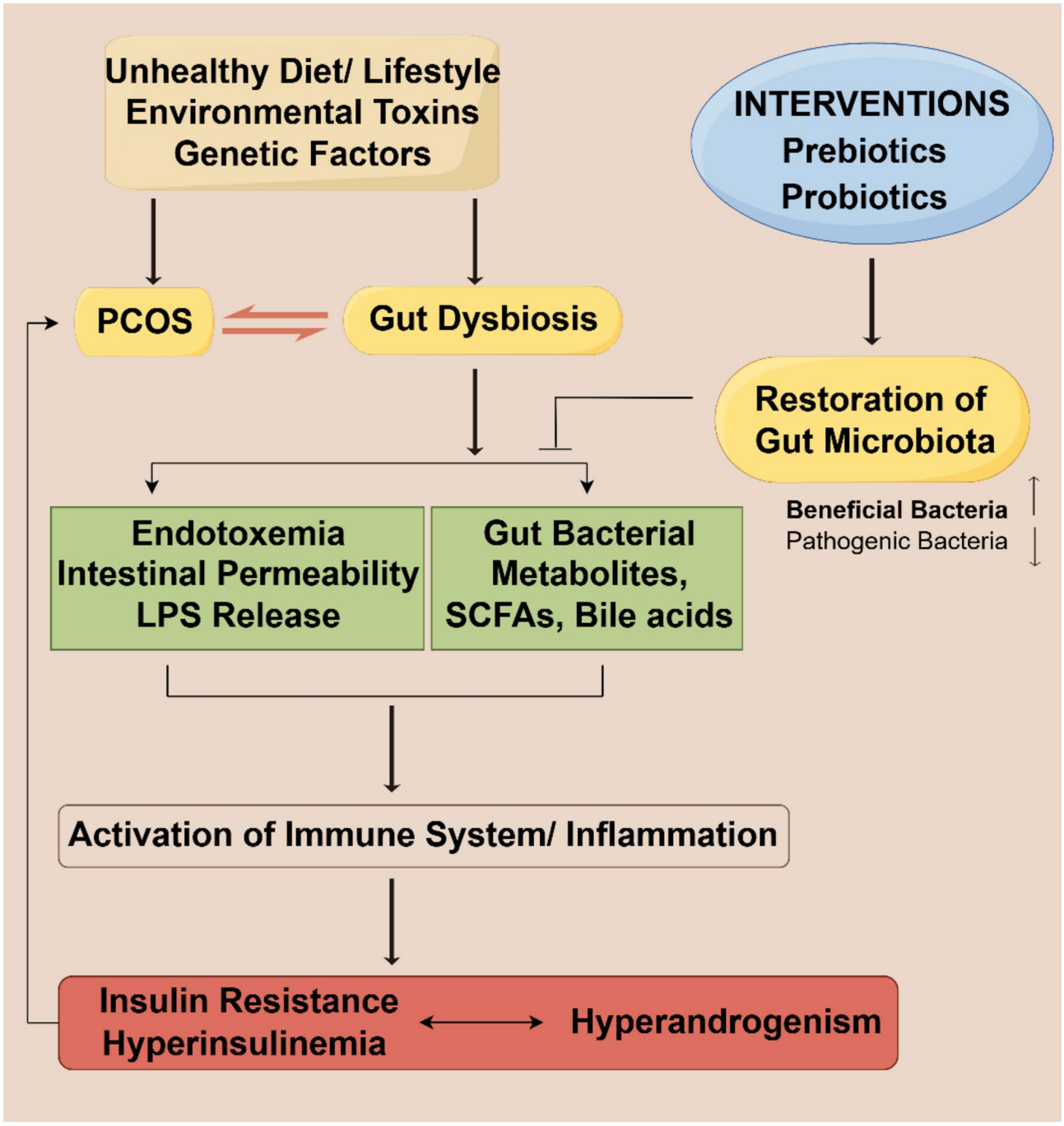

Fig. 3 In women with PCOS, supplementation with probiotics or Biostime, which is made up of probiotics, may regulate the gut microbiota. Increase the number of probiotics in the gut and reduce the number of conditioned pathogens. Altered metabolic levels in the gut, as well as intestinal permeability and LPS release, thereby reducing inflammation in the body and alleviating PCOS. By Figdraw

role in ovarian cancer, with Proteobacteria being more prevalent in cancer patients than in healthy women. Contrastingly, Firmicutes are predominant in healthy women compared to cancer patients. The estrogen-gut axis is vital for estrogen metabolism and utilization, but dysregulation, which may involve certain bacteria, such as Firmicutes, Actinobacteria, and Proteobacteria, is linked to ovarian cancer. Additionally, microorganisms associated with sexually transmitted diseases can impact the onset and progression of ovarian malignancies. Overall, microbes and their metabolites are considered incidental factors that increase the risk of ovarian cancer [24].

The gut microbiota significantly affects the environment in your digestive system. It also interacts with

hormones such as estrogen, androgens, and insulin, thereby influencing the reproductive endocrine system. The relationship between estrogen levels and the gut microbiota is two-way. This means that estrogen regulates the gut microbiota, and vice versa. Estrogen is crucial for the development and maintenance of the female reproductive system. It mainly acts on the lower female reproductive tract, where it increases epithelial thickness, glycogen concentration, and mucus secretion, in addition to promoting the abundance of lactic acid bacteria. Changes in estrogen levels are linked to conditions like endometrial cancer (particularly Type I), endometriosis, and uterine fibroids. Gut bacteria such as E. coli, Bacteroides fragilis, and Streptococcus agalactiae can uncouple glucuronic acid, leading to the reabsorption of active estrogens, this increases their affinity for estrogen beta (ER-β) receptors and may impact tumor formation in the reproductive system [76].

A study that investigated the relationship between microbiota and gynecological cancers indicated that gut microbiota is strongly associated with the development of some cancers that affect females. The results from the study also highlighted that microbiota products such as lipopolysaccharides can directly promote the production of pro-inflammatory cytokines and increase tumor tolerance of ovarian cancer cells [81]. In addition, the well-studied theory of dysbiosis of the PCOS gut microbiota has also been implicated in the development of multiple ovarian microcysts [82, 83]. Zhou et al. reported that the diversity and abundance of microbiota in ovarian cancer tissue is significantly reduced when compared to normal fallopian tube tissue. This suggests a link between microbiota and ovarian cancer [84].

Further research suggests two primary mechanisms through which the gut microbiota interfere with estrogen levels and ultimately contribute to the development and progression of ovarian cancer. The first mechanism is the disruption of hepatic-gut estrogen circulation. In this case, the gut microbiota can influence the circulation of estrogen between the liver and the gut, thereby impacting estrogen levels in the body. The second mechanism is the alteration of β-Glucuronidase activity. In this case, the gut microbiota affects the secretion of β-glucuronidase, an enzyme that increases estrogen activity. Higher estrogen levels may enhance gene transcription and mitotic activity, possibly leading to tumor development. Additionally, high β-glucuronidase activity may cause carcinogens to be produced, further promoting tumorigenesis (Fig. 4) [85].However, this mechanism is still highly controversial. The study also raises the possibility of using microbes as therapeutic tools to enhance immunity and improve anti-tumor responses. It further highlights the potential of using gut microbiota as a novel biomarker for cancer.

Wahid et al. have demonstrated that balancing the microbiome composition of gynecological cancers is a promising therapeutic target [8]. Lactobacillus can lower pH, produce bacteriocins, and competitively exclude other bacteria. The use of prebiotics, probiotics, and fecal microbiota transplants with specific bacterial strains can aid in achieving and maintaining a balanced gut microbiota. These interventions may help to restore or enhance the microbial community, potentially supporting overall health and addressing various conditions that are linked to microbiota imbalances. A healthy microbiome can train and activate the body's immune response to target various gynecological cancers. Modulating the microbiome may also enhance immuno-oncology therapy.

Microorganisms trigger innate and adaptive immune system responses, and this may promote malignancy [86]. Inflammatory mediators such as cytokines and chemokines have a direct impact on tumors and contribute to several markers of cancer [87].Bacteria affect carcinogenesis in four ways: stimulating cell proliferation or death, disrupting immune system function, affecting host cell metabolism [88], and triggering genomic instability and DNA damage [89].

Bacteria use their components, products, and metabolism to interact with tissues and potentially influence cancer development. Ovarian cancer is one of the main causes of death related to gynecological cancers. Although surgery and platinum-based chemotherapy are standard treatments, most patients will relapse and die from the disease. Chambers LM et al. have shown that the use of antibiotics may affect the efficacy of chemotherapy and immunotherapy in patients with non-gynecological cancers. Through a retrospective single-institution cohort study (2009–2015), 424 newly diagnosed patients with ovarian cancer were included, all of whom received cytoreductive surgery and chemotherapy. The grouping results were patients who received antibiotic treatment, anti-Gram-positive bacteria antibiotics such as vancomycin, and those who did not receive antibiotic treatment. After statistical analysis, it was concluded that patients receiving antibiotic treatment significantly reduced progression-free survival and overall survival. The use of anti-Gram-positive antibiotics had a more significant impact on the survival of patients. Researchers have demonstrated that the use of antibiotics is associated with a shortened progression time of ovarian diseases and a deterioration in overall survival, affecting the response and resistance to platinum-based chemotherapy [90].The application of antibiotics can disrupt the balance of the gut microbiota. The destruction of the microbiota structure may lead to the aggravation of patients' symptoms or the occurrence of complications, affecting the ultimate survival time and treatment effect of patients.

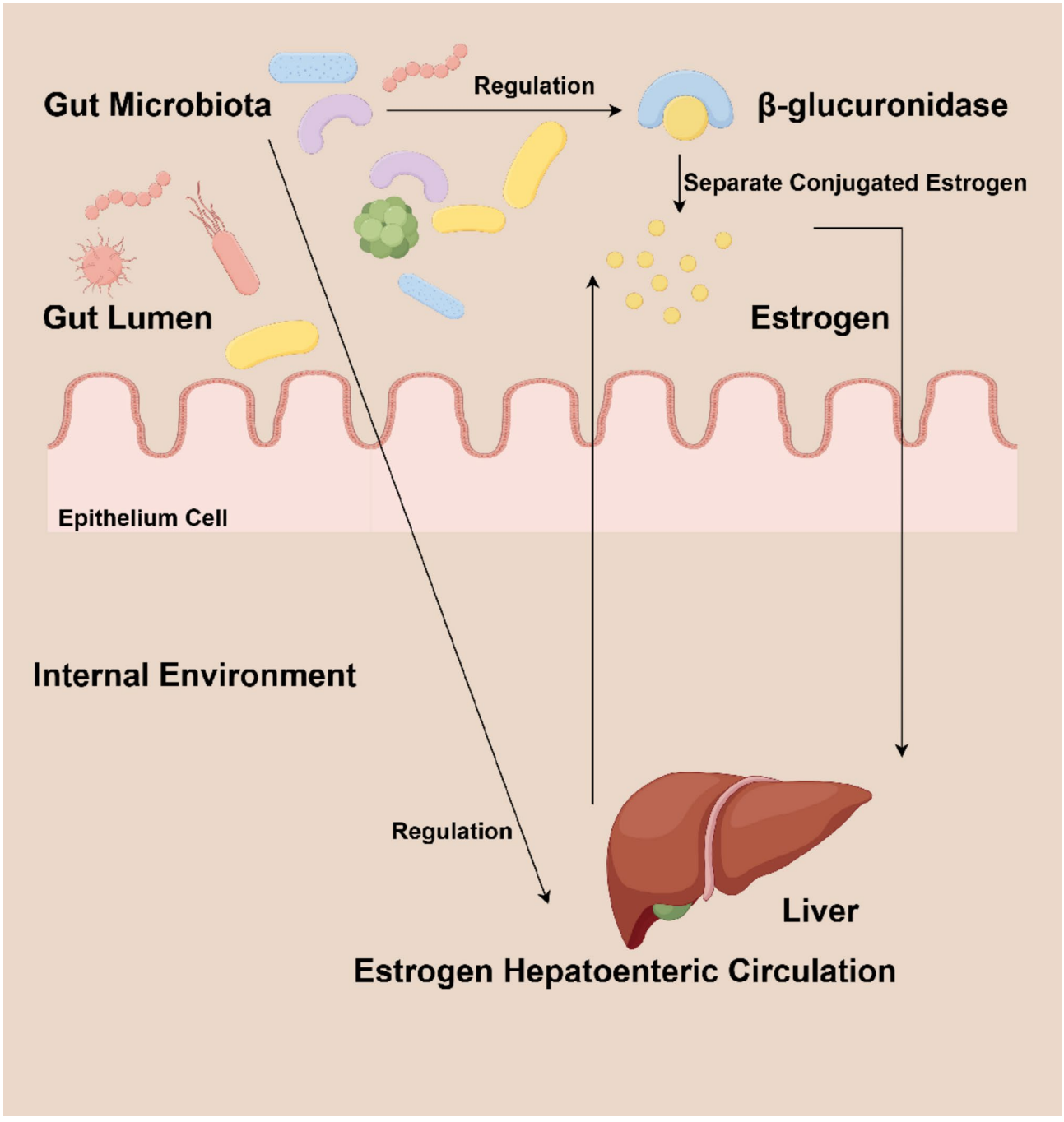

Fig. 4 Gut microbiota be involved in the development and progression of ovarian cancer by influencing estrogen levels, with the main mechanisms being (1) gut microbiota interfering with the hepatic-gut circulation of estrogen (2) gut microbiota interfering with the secretion of b-glucuronidase, thereby increasing estrogen activity. By Figdraw

Chambers LM et al. found that ovarian tumors in mice treated with antibiotics grew faster, resulting in a reduced efficacy of cisplatin and a shortened survival period of mice. Researchers believe that antibiotics significantly disrupt the diversity of the gut microbiota, reduce non-drug-resistant bacterial species, and increase drug-resistant bacteria such as Enterobacteriaceae. Chambers LM et al. transplanted the gut microbiota of control group mice into antibiotic-treated mice, which restored cisplatin sensitivity and prolonged survival. Metabolite detection revealed that antibiotics reduced the metabolites of gut microbiota in plasma (such as indole-3-propionic acid and indoleophenol sulfate), and gut microbiota transplantation could partially restore the levels of these

metabolites. Antibiotics lead to drug resistance by reducing DNA damage (down-regulation of 53BP1), enhancing repair (up-regulation of BRCA1), and promoting angiogenesis (up-regulation of CD31). Meanwhile, RNA sequencing revealed that the expression of stem cell-related genes (such as SOX2 and WNT7a) in tumors treated with antibiotic was upregulated, and the epithelial-mesenchymal transition and hypoxia pathways were activated. The research supports the role of the intestinal microbiota in inhibiting tumor growth and maintaining chemotherapy sensitivity, suggesting that antibiotics should be used with caution in clinical practice to avoid disrupting the microbiota. Meanwhile, this also suggests that microbiota transplantation or metabolite intervention may be a new strategy to overcome platinum resistance [91].

The microbiome's role in tumor development, particularly estrogen-mediated cancer, is of great interest. Microbes that are associated with cancer can target the Wnt/β-catenin signaling pathway in several ways. Bacteria may attach to epithelial cells through FadA adhesion, and this allows them to invade the host tissue and induce inflammatory responses that contribute to carcinogenesis. FadA activates β-catenin by binding to E-cadherin on the surface of the host cell. This interaction causes differential regulation of inflammatory processes and promotes carcinogenic responses. This stimulates cell growth and supports the development of cancer. Signaling cascades and receptor recognition patterns may be involved in breaking down the boundary between host cells and microbes. The NF-κB and STAT3 signaling pathways are crucial in regulating chronic inflammatory feed-forward loops that are linked to cancer development [92–94]. These pathways contribute to sustained inflammation, which can aid tumorigenesis. Additionally, susceptibility to HIV significantly increases when the vaginal epithelial barrier is disrupted, often due to the influence of vaginal bacteria. These bacteria play a key role in enhancing the secretion of pro-inflammatory cytokines during the epithelial cell response to HIV, thereby exacerbating the infection and its effects [95].

Summary and outlook

Increasingly more research has explored the gut microbiota and its potential effects on human health. Studies indicate that alterations in the gut microbiota may be associated with the development and progression of various diseases (Fig. 5). Notably, emerging evidence suggests a strong link between gut microbiota dysbiosis and ovarian-related infertility, possibly mediated through systemic inflammation, hormonal imbalance, and metabolic disturbances [96]. Empirical evidence from animal models provides strong support for the role of the microbiome in chronic disease conditions. Human diseases are consistently linked to fecal microbiota, with recent systematic reviews highlighting parallel disruptions in both gut and genital tract microbiomes in fertility disorders. The microbiota of diseased individuals significantly differs from that of healthy individuals in terms of taxonomic composition, diversity indices, and/or functional values/abundance. The disease-associated changes in the microbiome are commonly known as the 'dysbiosis' microbiome domain. Identifying the etiological components of the complex microbiota responsible for pathology can be quite challenging. This is mainly due to the highly individualized nature of the community, which comprises bacteria, archaea, fungi, viruses, and protozoa. All these microorganisms, along with their metabolites, may significantly contribute to the development of diseases, either individually or in combination.

The studies that were highlighted and discussed in this review have clearly established a significant correlation between gut microbiota and ovarian disease. Various ovarian diseases have been observed to cause changes in microbiota. Moreover, animal studies have provided compelling evidence of the causal relationship between microbiota and ovarian disease, mainly through regulatory pathways, immunity, or pathogenic mechanisms. It's important to note that alterations in the gut microbiota may have potential benefits in disease treatment. Further evidence is needed to determine causality, concomitance, or unrelatedness to the disease.

The function of gut microbiota has become increasingly important to various medical fields in recent years. As a result, extensive research is being undertaken concerning the mechanisms of action through which the gut microbiota interferes with diseases. Moreover, the available methods for microbiota analysis have advanced.

Characterizing the gut microbiota in various ovarian disease populations provides insight into certain pathological mechanisms. Different drugs alter the gut microbiota, thereby presenting a link and potential target for pharmacological mechanisms of action. Using probiotics to regulate gut microbiota presents a safe and effective therapy for ovarian disease. The introduction of active health in China has made primary prevention of ovarian disease from the gut microbiota a possibility. Further research on the mechanism of action of the gut microbiota is crucial as it positively impacts human health.

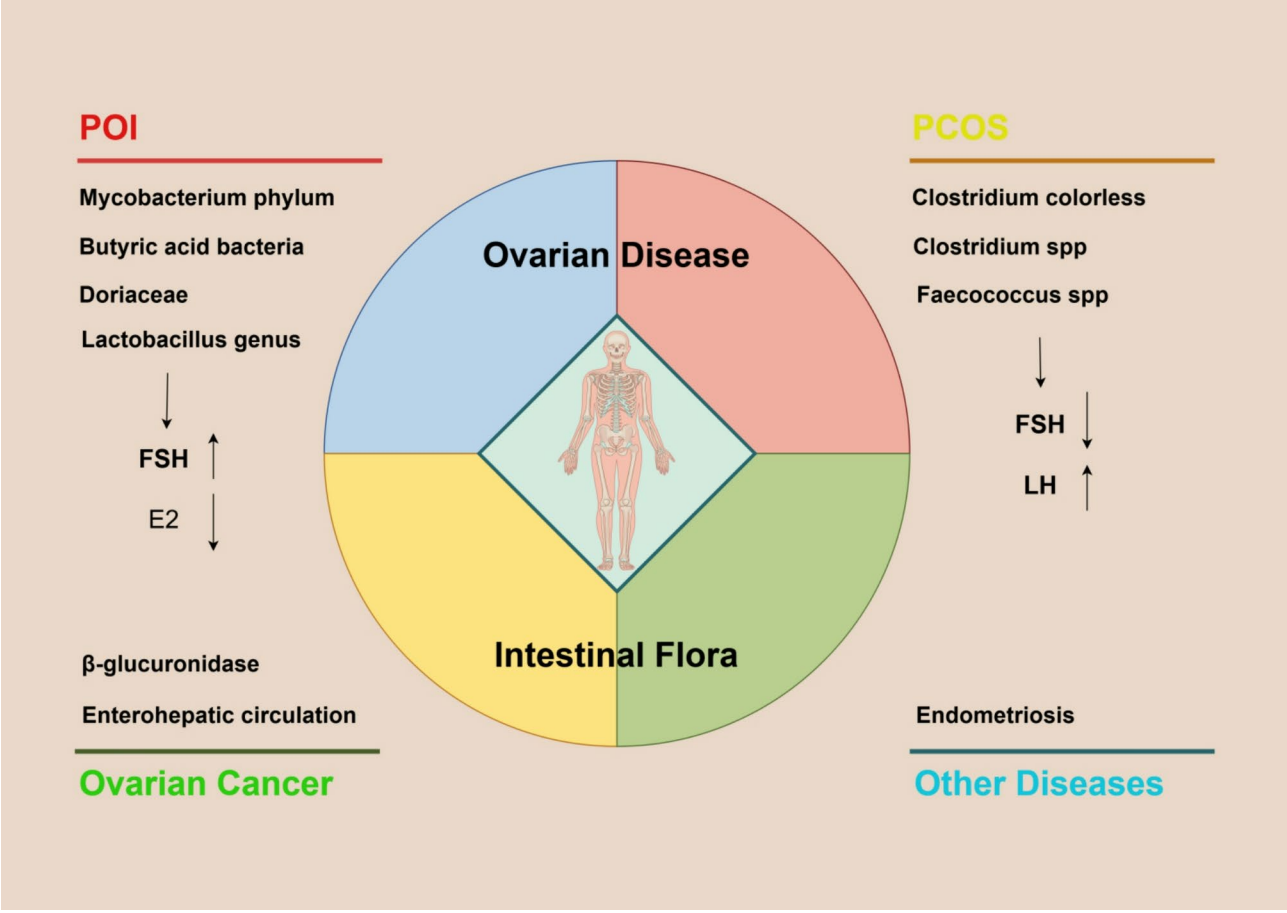

Fig. 5 POI: gut microbiota like Mycobacterium phylum, Butyric acid bacteria, Doriaceae, Lactobacillus genus are more abundant in the POI patients. PCOS: gut microbiota like Clostridium colorless, Clostridium spp and Faecococcus spp are more abundant in the POI patients. Cancer: gut microbiota interfering with the hepatic-gut circulation of estrogen and secretion of b-glucuronidase, elevating estrogen activity. By Figdraw.

Abbreviations

POI	Premature ovarian insufficiency
PCOS	Polycystic ovary syndrome
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
LBP	Lycium barbarum polysaccharide
EA	Electroacupuncture
VCD	4-Vinylcyclohexene diepoxide
LDA	Linear discriminant analysis
COG	Clusters of orthologous groups
APS	Astragalus polysaccharide
DHEA	Dehydroepiandrosterone
BS	Butylated starch
FMT	Fecal microbiota transplantation
E2	Estradiol
LPS	Lipopolysaccharide
SCFAs	Short-chain fatty acids

Author contributions

Ju Shan and Kang Zhenyang wrote the main manuscript text, while Wang Huiping and Ai Lianzhong were responsible for the communication tasks and funding; Yang Liya, Xia Yongjun, Guo Yiming and Qi Mingkang were responsible for the revision and literature search. Sui Li and Yan Hongli were responsible for providing guidance and logical revisions to the review.All the authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

Clinical Trial Number

Not applicable.

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