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Review Article

Microbial harmony in female reproductive health: exploring the impact of intestinal flora on ovarian function and disease pathogenesis

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Abstract: The intestinal microbiota is vast in type and quantity and it plays a critical role in regulating various physiological functions in the host, including intestinal function, immune response and energy metabolism. Existing research shows that intestinal flora is associated with various hormones, cell cycles and ovarian function-related diseases in the female ovaries. Certain microorganisms within the intestinal flora can modulate the levels of hormones secreted by the ovary, such as estrogen and androgens. Furthermore, an imbalance in the gut microbiota can result in altered hormone levels in the host, potentially leading to related diseases. Studies have found that a variety of ovarian function-related diseases are closely related to intestinal flora, such as polycystic ovary syndrome (PCOS), ovarian insufficiency (POI), endometriosis (EMS) and ovarian cancer. Importantly, ovarian function-related diseases are notably difficult to diagnose early and often require prolonged treatment for effective management. The microbiota and its metabolites in patients with ovarian function-related diseases and cancers can serve as valuable biomarkers for early diagnosis, offering novel strategies for disease screening, treatment stratification, and prognosis.

Keywords: Intestinal flora, estrogen, polycystic ovary syndrome, premature ovarian insufficiency, endometriosis, ovarian tumors

Introduction

The ovary is one of the crucial organs within the female reproductive system and it has reproductive and endocrine functions [1]. Normal ovarian function has been proven to be closely related to women's health, and ovarian dysfunction can cause a variety of diseases, such as PCOS (polycystic ovary syndrome), POI (premature ovarian insufficiency), infertility, osteoporosis and cardiovascular problems [2-4]. PCOS is the most common ovarian dysfunction which can affect 8-13% of women of childbearing age worldwide with 70% of cases remaining undiagnosed [5]. Diseases related to ovarian dysfunction are high-risk factors for humans that suffer from diabetes, endometrial cancer, cardiovascular and cerebrovascular diseases [6, 7] and they seriously harm human health. The pathogenesis of diseases related to ovarian dysfunction is complex and it is affected by a variety of factors, such as genetics, inflammation, intestinal flora, endocrine hormones and environmental factors [8, 9]. In recent years, with the study of intestinal flora attracting extensive attention, some researchers began to pay attention to the effect of intestinal flora on ovarian function [10], especially the role of intestinal flora in ovarian function-related diseases.

Intestinal flora is the community of microorganisms present in the human intestine, including bacteria, fungi, viruses and other microorganisms [11]. The intestinal flora coexists with the human body and forms a complex and huge ecosystem. Intestinal flora plays an extremely important role in the growth and development

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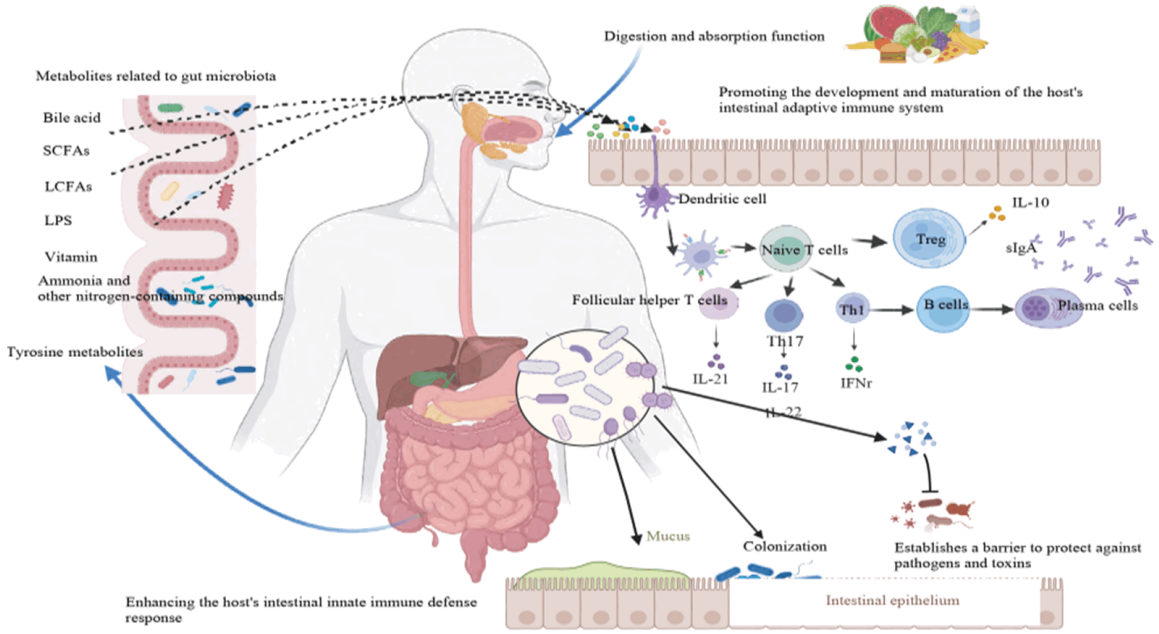

Figure 1. Function of intestinal flora.

of the human body, participating in nutrient supply, metabolic regulation, immune regulation and other physiological processes [12-14] (**Figure 1**). Specific bacterial communities in the intestine can participate in the metabolism of estrogen through the microbial-intestinal-ovarian axis which can affect the hormone expression level and function of the ovaries [15]. Research has shown that women's exposure to zearalenone significantly alters the intestinal flora of their offspring which can lead to changes in Bacteroidetes, Proteobacteria, and Firmicutes [16]. These changes cause adjustments in glutathione metabolism and antioxidant enzyme activity in the ovaries that in turn affects the development of oocytes in the offspring.

The intestinal flora is vital for the maturation and fertilization of female follicles and oocytes, as well as for embryo migration and implantation. At present, research on ovarian function mainly focuses on the biological functions of the ovary and various ovary-related diseases, some studies have shown that intestinal flora were closely related to patients' metabolic indicators compared with healthy controls [17], such as insulin resistance and body weight. Intestinal flora plays a crucial role in the occurrence and regression of female reproductive endocrine diseases such as PCOS and premature ovarian insufficiency (POI) [2]. Intestinal flora can interact with a variety of hormones and plays an important role in the female reproductive endocrine system, such as estrogen, androgens, and insulin [18]. A study on intestinal flora found that Clostridium can transform glucocorticoids to androgens [19]. Therefore, it is imperative to conduct in-depth research on the relationship between ovarian function and intestinal flora.

The impact of intestinal flora on hormonal regulation and ovarian function

Intestinal flora and estrogen

Estrogen is a crucial hormone in the human body and is involved in various vital physiological functions, such as cell proliferation and death, lipid metabolism, energy balance, glucose metabolism, immune and cardiovascular regulation, gametogenesis, reproduction and bone growth [20-22]. Research indicates that intestinal flora is influenced by estrogen and can also regulate estrogen levels through enterohepatic circulation [19]. Some intestinal flora can secrete β-glucuronidase which is an enzyme that converts estrogen into its active form and allows it to bind to estrogen receptors. Imbalances in intestinal flora can alter β-glucuronidase levels that can lead to an

excess or deficiency of free estrogen and potentially causing estrogen-related diseases [23]. A reduced diversity of gut flora can decrease β-glucuronidase activity which can lower estrogen levels and contributing to conditions like obesity, metabolic syndrome, cardiovascular disease, and cognitive decline [24]. Conversely, an increased presence of β-glucuronidase-secreting bacteria can raise estrogen levels that possibly trigger endometriosis (EMS) and cancer [25, 26]. Studies have also found that specific gut bacteria, such as *Clostridium*, *Ruminococcus*, *Bacteroides* and *Staphylococcus* are correlated with varying levels of estrogen and its metabolites in the body [27]. Additionally, the liver produces conjugated estrogens that intestinal bacterial enzymes convert into their active forms which influence overall estrogen levels and their physiological effects.

A study on the E_2 (estradiol) hormone in women found that those with elevated E_2 levels had significantly increased diversity in their intestinal flora, specifically in species like *Slackia* and *Butyricimonas* [28]. In men and postmenopausal women, urinary estrogen levels strongly correlate with gut microbiota richness and α-diversity, with intestinal flora diversity being positively associated with the proportion of urinary estrogen metabolites [29]. Previous research has established a link between estrogen and the development of various cancers, including endometrial, ovarian, prostate, and breast cancer [30]. A recent investigation on breast cancer highlighted estrogen's ability to induce DNA double-strand breaks in the estrogen receptor binding region, which can contribute to breast cancer development [30]. Furthermore, some intestinal flora plays a key role in the onset and progression of these cancers. A study examining the intestinal flora of adenocarcinoma patients found increased diversity and quantity of microorganisms such as *Rikenellaceae*, *Alistipes*, and *Lachnospira* compared to healthy individuals [31].

Intestinal flora and androgens

Androgen levels are one of the basic prerequisites for healthy women [32]. Androgen deficiency may cause individuals to experience symptoms of sexual dysfunction, such as decreased sexual desire, loss of sexual response, or weakened sexual arousal [33]. Women with POI not only lack estrogen but may also have reduced ovarian androgens due to ovarian cortical atrophy [9]. Studies have found that Clostridium can synthesize androgens using glucocorticoids as raw materials [34]. Some bacteria can also produce 5α reductase to convert testosterone into more active dihydrotestosterone [35]. Some intestinal flora regulates androgen levels through Deglucuronidation to release free dihydrotestosterone from the glucuronide conjugate [36]. Androgen levels can be affected by intestinal flora, and androgens in the host can also affect the composition of intestinal flora.

Hyperandrogenism (HA) is a key feature of PCOS that can lead to symptoms like acne, hirsutism and androgenic alopecia [37]. Various intestinal floras can produce enzymes involved in androgen metabolism, potentially affecting androgen levels in the body, while serum androgen levels can also impact gut flora composition. There is a strong link between gut microbiota and HA. Studies in patients with POI show that an increase in *Campylobacter*, *Desulfobacteria*, and *Bacteroidetes* can raise testosterone levels, while more *Proteobacteria*, *Chloroflexi*, and *Actinobacteria* can lower them [38]. Androgens, such as testosterone, support early follicular development and help improve ovarian reserves in women with reduced ovarian function [39]. Low testosterone levels have been linked to the development of EMS and POI [40]. Research also indicates that gut microbiota composition strongly correlates with circulating gonadal steroid levels, especially testosterone. For example, excessive prenatal testosterone injections in female rats led to reduced abundance of *Akkermansia*, *Bacteroidetes*, *Lactobacilli*, and *Clostridium* in their offspring, indicating an interaction between androgens and intestinal flora [41].

Intestinal flora and the hypothalamus-pituitary-ovarian (HPO) axis

Communication between intestinal flora and the brain forms a physiological network known as the "gut-brain" axis, involving the central nervous system (CNS), enteric nervous system (ENS), endocrine and immune systems [42] (**Figure 2**). This axis is closely linked to the neuroendocrine regulation of the hypothalamus-

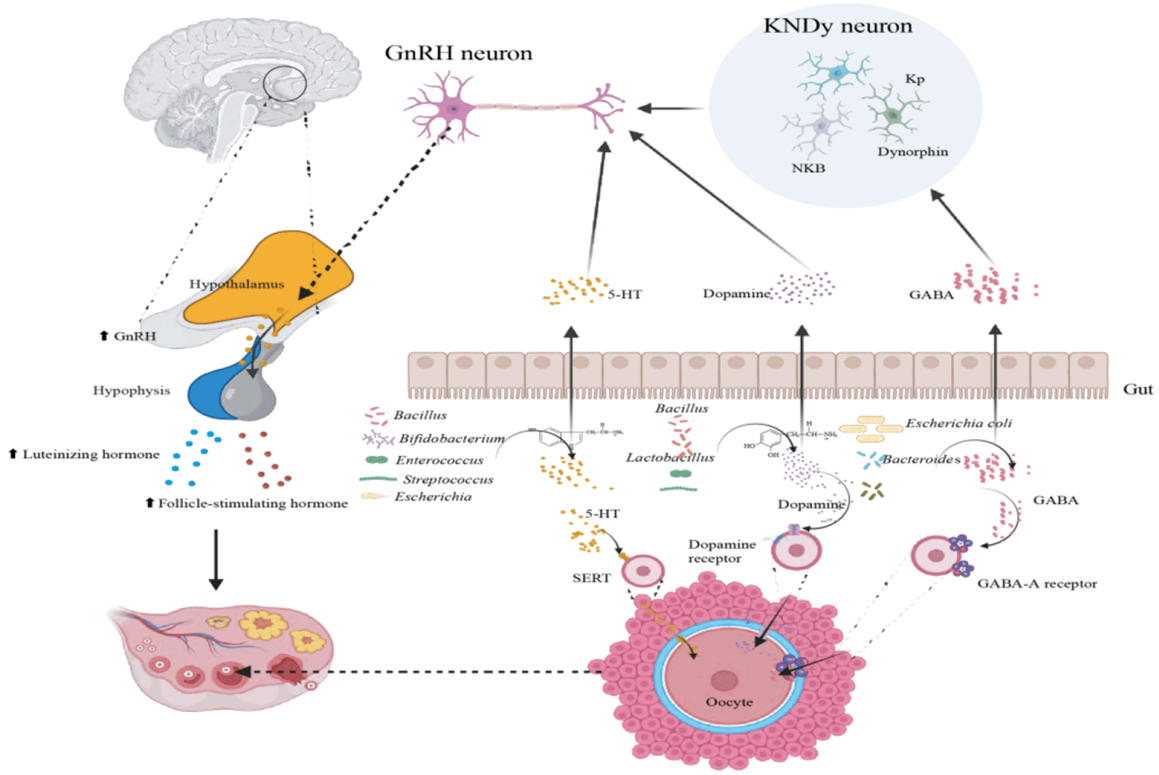

Figure 2. Gut-microbiota-brain axis and hypothalamus-pituitary-ovarian (HPO) axis.

pituitary-ovarian (HPO) axis which is part of the hypothalamus-pituitary-gonadal (HPG) system [43]. The pituitary gland, located at the brain's base, receives signals from the hypothalamus via gonadotropin-releasing hormone (GnRH) to secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH). FSH stimulates follicle maturation in the ovaries, leading to estrogen production, which then inhibits FSH secretion and triggers LH secretion. High LH levels ultimately lead to ovulation. Increasing evidence suggests that intestinal flora communicates with the CNS through the "gut-brain" axis, potentially influencing the HPO axis by modulating neurotransmitter synthesis and release [44].

Key neurotransmitters such as γ-aminobutyric acid (GABA), 5-hydroxytryptamine (5-HT) and dopamine (DA) can impact ovarian function through neural pathways [45]. Intestinal bacteria like *Streptococcus*, *Enterococcus*, *Escherichia*, *Bifidobacterium*, and *Bacillus* can synthesize 5-HT, which regulates gonadotropin secretion by affecting GnRH neuron activity [46]. 5-HT is involved in ovarian hormone production, follicle maturation, and ovulation [47]. Additionally, 5-HT can induce germ cell production and initiate egg maturation. *Bacillus*, *Lactobacillus*, and *Streptococcus* can synthesize DA in vitro, and *Enterococcus faecalis* expresses enzymes involved in DA biosynthesis [48, 49]. *Bacteroidetes* and *Escherichia* produce GABA which can influences GnRH neurons and reproductive function [50]. Excessive GABA production by gut flora can interfere with KNDy (Kisspeptin Neurokinin B Dynorphin) neurons which can affect GnRH secretion, fertility, sex hormone levels and menstrual cycles [51].

Diseases related to intestinal flora and ovarian function

The human intestinal flora is primarily composed of three types: probiotics, neutral bacteria, and pathogenic bacteria [52]. Probiotics that mainly obligate anaerobic bacteria like *Bacteroides*, *Eurobacterium*, and *Bifidobacterium* play key roles in regulating intestinal flora, intestinal function and immune response, preventing intestinal infection, increasing mineral absorption and promoting bone health, regulat-

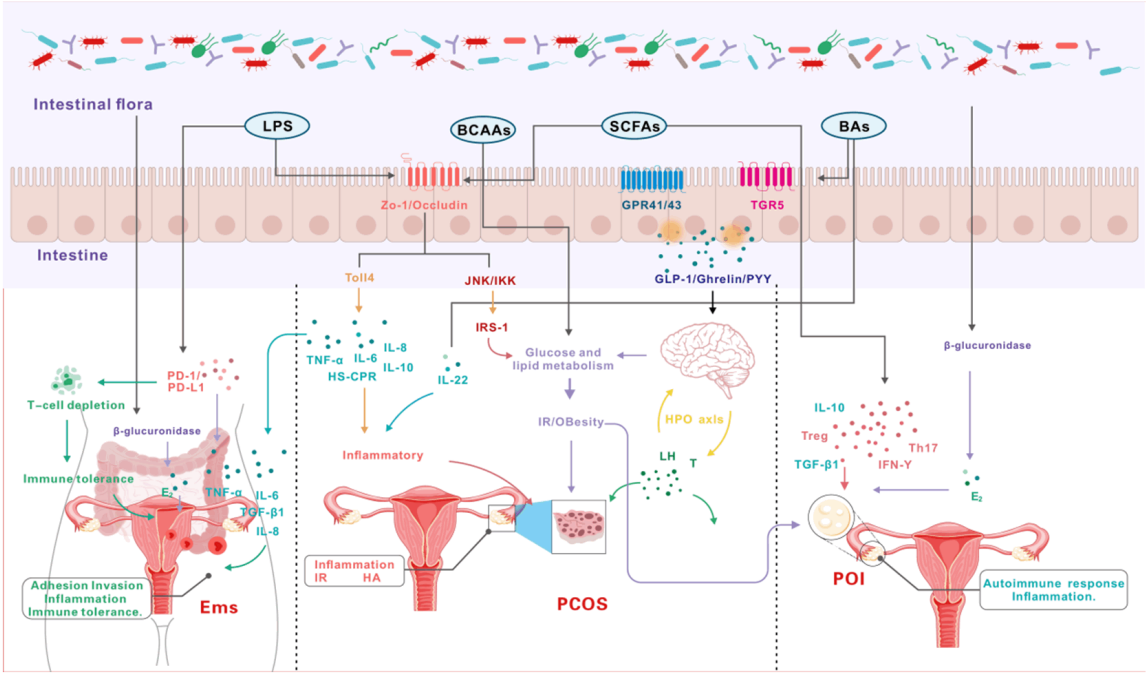

Figure 3. Molecular mechanism of diseases related to intestinal flora and ovarian function.

ing energy metabolism, maintaining weight and reducing obesity [52-54].

However, an imbalance in gut flora decreases the expression of ZO-1 (zonula occludens-1) and occludin in the intestinal mucosa, leading to increased intestinal permeability [55]. This increased permeability allows particles, bacteria and toxins to enter the bloodstream, potentially triggering chronic inflammation, insulin resistance (IR), and hyperandrogenism (HA) [56, 57]. Short-chain fatty acids (SCFAs) that are key metabolites produced by intestinal flora are crucial for energy supply, immune regulation, intestinal mucosal protection and appetite control [58]. Research indicates that imbalances in intestinal flora contribute to various diseases, including autoimmune disorders, neurodegenerative conditions, cancer and ovarian function-related diseases [59, 60]. Recent studies have focused on the connection between gut flora and ovarian function disorders like PCOS [61], POI [62] and EMS [63] (**Figure 3**; **Table 1**).

PCOS and intestinal flora

PCOS is the most common endocrine disorder with diverse clinical manifestations [2]. Menstrual disorders, enlarged and polycystic ovaries, HA, IR, hirsutism, oligomenorrhea and no ovulation are the main clinical features of PCOS [64]. A low-grade chronic inflammatory response is a key factor in follicle development disorders, with inflammatory markers like tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) playing a role [65]. Patients with PCOS experience persistent low-grade inflammation which contributes to both its pathology and associated metabolic disorders. Diamine oxidase (DAO) is a highly active enzyme in the intestinal mucosa, and lipopolysaccharide (LPS) is a bacterial metabolite [66]. In healthy individuals, LPS levels remain relatively low, and both DAO and LPS are used clinically to assess intestinal barrier function [67]. In PCOS patients, serum DAO levels are significantly elevated, particularly in those with obesity-related intestinal flora imbalance. This imbalance can lead to the overexpression of zonulin, increasing intestinal permeability [68]. Higher permeability allows LPS to enter the bloodstream, binding to receptors and triggering a chronic inflammatory response that can exacerbate PCOS [69].

Studies have found a link between specific intestinal flora and PCOS. Beneficial bacteria like *Bifidobacterium*, *Blautia*, and *Holdemania*

Table 1. Changes in intestinal flora content in the host and diseases related to ovarian function

Disease	Species	Intestinal flora	
		Increase	Descend
PCOS	Human	*Bacteroides Escherichia coli*	
	Mouse	*Firmicutes*	*Bacteroidetes*
POI	Human	*Firmicutes, Brucella, Faecalis*	*Bacillus, Bacteroides*
	Mouse		*Akkermansia, Bacteroidetes, Lactobacilli, Clostridium*
EMS	Human		*Leptothrix, Pasteurella, Gardnerella*
	Mouse	*Actinobacillus, Firmicutes, Bifidobacteria, Burkella*	

are linked to a reduced risk, while an increased abundance of *Lachnospiraceae* correlates with adverse PCOS outcomes [70]. PCOS patients show decreased alpha diversity in intestinal flora with notable shifts in microbial abundance. Alterations in beta diversity can also impact intestinal barrier function and inflammation, such as by increasing the relative abundance of *Porphyromonas* which can affect intestinal permeability [71]. In individuals with PCOS, especially those exhibiting insulin resistance, the diminished abundance of beneficial bacteria such as Prevotella correlates with disruptions in sex hormone balance and increased inflammatory responses [72]. This imbalance of intestinal flora impairs intestinal barrier function and exacerbates PCOS symptoms.

IR is a key clinical feature of PCOS, and abnormal glucose and lipid metabolism are common in these patients [73]. Studies suggest that intestinal flora imbalance may contribute to IR and compensatory hyperinsulinemia in PCOS, with *Actinobacteria* showing a strong correlation with the insulin resistance index (HOMA-IR) [74, 75]. Patients with IR exhibit a more significant reduction in intestinal flora diversity, an increase in *Bacteroidetes*, and a notable decrease in *Firmicutes* [76]. Certain bacterial groups are closely related to blood lipids, glucose levels, endocrine and metabolic disorders, potentially playing a role in alleviating PCOS symptoms, such as *Proteobacteria*, *Actinobacteria* and *Chloroflexi* [77].

HA is a core pathological feature of PCOS, where excessive androgens disrupt follicle development that can lead to anovulation or infrequent ovulation [78]. Some studies have found that as the diversity of intestinal flora decreases, the balance of intestinal commensal bacteria is disrupted which may lead to corresponding changes in the abundance of some intestinal flora related to testosterone and metabolic disease markers [79]. In HA conditions, PCOS patients often exhibit gut flora imbalances. In a study using 5α-dihydrotestosterone (5α-DHT) to establish a PCOS rat model, both regular and high-fat diet groups demonstrated increased androgen levels and changes in ovarian morphology [80]. Compared to controls, these rats showed dysregulated gut flora, elevated inflammatory markers, and higher HOMA-IR than healthy rats. These findings suggest that gut flora imbalance and HA may interact in a vicious cycle, exacerbating the clinical symptoms of PCOS.

POI and intestinal flora

Primary ovarian insufficiency (POI) is characterized by the decline of ovarian function in women under the age of 40 and is often accompanied by hypergonadotropic amenorrhea resulting from estrogen deficiency [9]. Research on the gut microbiome in POI patients has revealed alterations in the microbial spectrum, including a decrease in *Firmicutes*, *Brucella*, and *Fecalobacteria*, alongside an increase in *Bacteroidetes* compared to healthy individuals [81]. Additionally, POI patients exhibited significantly reduced estradiol levels. Correlation analysis indicated associations between certain intestinal flora and serum levels of estradiol, FSH, luteinizing hormone, and anti-Müllerian hormone. POI patients not only lack estrogen but may also experience reduced ovarian androgens due to cortical atrophy. A meta-analysis further demonstrated that women with POI are at risk of lower concentrations of total testosterone, dehydroepiandrosterone sulfate and androstenedione [82].

The pathogenesis of POI is complex, but analyses have found that 10% to 55% of POI patients also suffer from autoimmune diseases

[83]. Among POI cases, 4% to 30% may develop autoimmune conditions, such as autoimmune thyroiditis, type 1 diabetes, Addison's disease, and systemic lupus erythematosus [83-85]. The intestinal flora plays a key role in autoimmune processes, including immune system regulation, immune cell development, anti-inflammatory effects, intestinal barrier function and immune tolerance modulation [86]. Autoimmune diseases in POI patients are related to the regulation of cytokines such as Treg, IFN-γ, and Th17 [87]. Short-chain fatty acids (SCFAs) produced by gut flora promote the expression and differentiation of Treg cells, facilitating anti-inflammatory responses that regulate immune function [88]. Notably, POI patients exhibit a significant increase in Treg cells after treatment, indicating changes in their immunomodulatory effects [89].

EMS and intestinal flora

EMS is a chronic estrogen-dependent disease caused by the retrograde entry of shed endometrial tissue into the lower abdominal cavity [90], and its incidence tends to be younger and rising [91]. The abnormal endocrine microenvironment of EMS lesions is considered to be its main feature [92]. Estrogen directly promotes anti-apoptotic and proliferative effects in EMS lesions, contributing to a pro-inflammatory environment [93]. Increased estrogen synthesis is linked to various enzymatic pathways, and intestinal flora can regulate estrogen levels through the secretion of β-glucuronidase [94]. Intestinal flora imbalance can lead to increased β-glucuronidase activity which can lead to increased estrogen levels. This rise in estrogen triggers the invasive growth of ectopic endometrial tissue, accelerating the proliferation of endometriotic lesions. Intestinal flora can also regulate estrogen levels by producing SCFA [95]. Butyrate is one of the more abundant SCFAs, and butyrate can regulate the synthesis of progesterone and E_2 in primordial germ cells (PGCs) through the cAMP signaling pathway to promote the synthesis of estrogen. In vitro studies indicate that low concentrations of butyric acid stimulate progesterone secretion in PGCs, whereas higher concentrations significantly inhibit progesterone production [96].

The abnormal inflammatory microenvironment accelerates the colonization and invasion of ectopic endometrial tissue [92]. Normally, the intestinal flora maintains epithelial integrity, offering protection against bacterial invasion while exhibiting complex antibacterial and immunomodulatory functions. However, an imbalance in the intestinal flora can lead to the production of endotoxins like lipopolysaccharides (LPS) by Gram-negative bacteria [66]. LPS promotes the expression of adhesion molecules between the endometrium and pelvic peritoneal cells, facilitating ectopic endometrial adhesion and invasion. Dysbiosis in EMS patients can further trigger an inflammatory response, increasing the number of peritoneal macrophages [97]. These macrophages secrete large amounts of TGF-β that can promote the secretion of extracellular matrix proteins like fibronectin and collagen [98]. Additionally, an imbalance in the intestinal flora in EMS patients is associated with a significant increase in *Streptococcus bovis*, which releases toxic proteins with pro-inflammatory effects [99]. The persistent inflammation caused by the shedding of endometrial tissue disrupts the diversity of the gut microbiota and impairs intestinal barrier function. This disturbance creates a vicious cycle that contributes to disease progression and exacerbates gut dysbiosis.

The reflux of endometrial tissue into the abdominal cavity as foreign matter in healthy women triggers a response from immune cells in the peritoneal fluid [100]. This immune response clears up endometrial tissue or cells that cause reflux of menstrual blood. However, EMS patients have immune tolerance and refluxed EMS tissues or cells can escape immune clearance [101]. The escaped EMS tissue or cells can grow and develop into ectopic lesions in the pelvis or abdomen. Studies have found that a large number of bacterial endotoxins caused by intestinal flora disorders continue to stimulate and activate immune signaling-related pathways that leads to the overexpression of PD-1 and PD-L1 [102]. This induces immune T cell exhaustion and contributes to the occurrence and development of EMS.

Ovarian tumors and intestinal flora

Ovarian tumors are the most common gynecological tumors in women and the leading cause of gynecological cancer deaths worldwide [103]. The embryonic development and compo-

sition of ovarian tissue is complex that can result in many histological types, more than 30 [104]. Patients with ovarian tumors often exhibit heightened sensitivity to changes in the intestinal flora and may present with gastrointestinal symptoms in the early stages of the disease, such as abdominal pain, bloating, indigestion, constipation and early satiety [105, 106].

LPS, lysophospholipids and tryptophan are all related products of intestinal flora metabolism, and these substances play a key role in the development of ovarian cancer [107, 108]. LPS can stimulate Toll-like receptor 2 (TLR2), TLR4 and TLR5, activate phosphatidylinositol 3-kinase (PI3K) signaling, matrix metalloproteinases (MMP)-related family expression and tumor-associated macrophages and induce epithelial-mesenchymal transition (EMT) [109]. Lysophosphatidylserine and lysophosphatidylserine have been shown to induce protein kinase B (Akt), mitogen-activated protein kinase (MAPK) and Ca^{2+} signaling [110] which can upregulate the expression of angiogenesis and induce the proliferation, migration and invasion of ovarian cancer cells. Tryptophan as an energy source can support the growth of Lactobacillus, inhibit the expansion of pathogenic bacteria, regulate mucosal immunity by activating aryl hydrocarbon receptor (AHR) and pregnane X receptor (PXR) [111].

A study found that after using antibiotics to deplete the intestinal flora of human ovarian adenocarcinoma cell SKOV-3 cells in nude mice [112], the growth rate of ovarian cancer tumors was significantly accelerated which confirmed that dysbiosis of the intestinal microbiota promotes the progression of ovarian cancer. In addition, a study conducted high-throughput sequencing of 16S ribosomal ribonucleic acid (16SrRNA) on the peritoneal fluid of 10 patients with ovarian cancer and 20 patients with benign ovarian tumors and found that the peritoneal fluid of ovarian cancer patients was rich in gram-negative bacteria derived from the intestinal tract, and 18 microorganisms were identified as new markers for ovarian cancer [113].

Intestinal flora treats ovarian function-related diseases

Probiotics are active microorganisms that provide health benefits to the host, primarily including beneficial bacteria such as *Lactobacilli* and *Bifidobacteria* [114]. They are involved in various physiological processes in the human body, including maintaining intestinal flora balance, regulating the immune system, preventing and treating antibiotic-induced dysbiosis, exhibiting anti-inflammatory effects, and contributing to energy metabolism and weight management [115, 116]. Probiotics have been extensively studied and are widely used to treat a range of health conditions, particularly those related to intestinal health, immune system regulation, diarrhea, digestive issues, allergic diseases, metabolic disorders, and psychiatric conditions [114, 117]. The intestinal flora is known to be associated with several ovarian function-related diseases, such as polycystic ovary syndrome (PCOS), premature ovarian insufficiency (POI), and endometriosis (EMS), playing a significant role in the onset and progression of these conditions.

Ovarian function-related diseases are often difficult to diagnose in their early stages [118]. Most of these diseases are chronic diseases with long treatment and follow-up management cycles, making them difficult to treat with conventional treatments [119]. A study on the effects of probiotics in patients with PCOS found that after 12 weeks of supplementation, there was a significant decrease in both body weight and body mass index, along with notable reductions in blood sugar and lipid levels [120]. Probiotics can influence the host's energy balance and metabolism by modulating the composition and quantity of the intestinal flora that can reduce body weight and BMI [121]. Given that PCOS patients are prone to insulin resistance and metabolic dysfunction, some research suggests that probiotic supplementation may also reduce insulin resistance in individuals with type II diabetes [122]. Studies using mouse models have found that probiotic supplementation can improve intestinal permeability, reduce plasma endotoxin levels, alleviate inflammation and decrease insulin resistance [122, 123]. The imbalance of intestinal flora in POI patients is one of the main characteristics. In a study of guinea pigs, pretreating them with probiotics restored beneficial bacterial species, butyric acid production, and defecation [124]. The combination of gut microbiota and probiotics can influence glucose metabolism through immune system modulation and

treat related diseases [125], through reduction of lipopolysaccharides and inflammation-causing bacterial endotoxins.

From 0% to 80% of patients with advanced ovarian cancer relapse within 2 years and develop chemotherapy resistance. Some studies have found that gut microbiota has a two-way effect in tumor chemotherapy and targeted therapy [126]. Microorganisms can mediate chemotherapy resistance and enhance antitumor activity. Studies have found that multidrug resistance proteins involved in paclitaxel resistance are downregulated upon TLR4 inactivation, further supporting the potential impact of the microbiota on chemotherapy resistance in ovarian cancer [127]. The microbiota affects the efficacy of commonly used drugs for ovarian cancer and has great potential to enhance immunotherapy responses.

Currently, fecal transplantation and probiotic supplementation are commonly used in the treatment of non-malignant diseases [128]. Research has found that changing the microbiota structure is expected to alleviate the adverse reactions of chemotherapy for ovarian cancer and provide new opportunities for its treatment [129]. In the treatment of platinum and anti-PD-1 monoclonal antibodies, combining probiotics can significantly improve the efficacy of ovarian cancer therapy [130]. Moreover, supplementation with *Ackermannia* or implantation of donor fecal bacteria with good drug response can reverse resistance to PD-1 therapy [131]. Antibiotics may have potential in treating ovarian cancer, but studies have been inconsistent in their conclusions. Chloramphenicol, salinomycin, and cisplatin were used in combination to inhibit tumor growth [132]. While combined treatment with ampicillin, vancomycin, neomycin and metronidazole promoted the growth and invasion of transplanted tumors in nude mice [133].

Conclusion

The ovaries are vital organs in the female reproductive system which can play a crucial role in maintaining overall health. This study focuses on the relationship between ovarian function-related diseases and intestinal flora in women with PCOS, POI and EMS. The findings suggest that an imbalance in intestinal flora can increase intestinal permeability, contributing to low-grade chronic inflammation, IR and HA. Imbalance of intestinal flora can affect the levels of estrogen and androgen that can promote the occurrence and development of PCOS, POI and EMS diseases. In ovarian cancer, the microbiota can also impact disease onset, progression and treatment response. While some studies have demonstrated that probiotics can be beneficial in treating ovarian function-related diseases, further research is needed to elucidate the specific mechanisms by which probiotics act in different conditions and to identify the most effective strains and treatment regimens. This study delves into the molecular mechanisms linking intestinal flora to ovarian function, highlighting that gut imbalance could be a contributing factor in these diseases. Additionally, the potential benefits of probiotics in treating ovarian function-related conditions and cancer offer a promising direction for future clinical applications.

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Disclosure of conflict of interest

None.

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References

[1] Richards JS and Pangas SA. The ovary: basic biology and clinical implications. J Clin Invest 2010; 120: 963-972.
[2] Rosenfield RL and Ehrmann DA. The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocr Rev 2016; 37: 467-520.
[3] Szeliga A, Maciejewska-Jeske M and Męczekalski B. Bone health and evaluation of bone mineral density in patients with premature ovarian insufficiency. Prz Menopauzalny 2018; 17: 112-116.
[4] Legro RS. Polycystic ovary syndrome and cardiovascular disease: a premature association? Endocr Rev 2003; 24: 302-312.

[5] Safiri S, Noori M, Nejadghaderi SA, Karamzad N, Carson-Chahhoud K, Sullman MJM, Collins GS, Kolahi AA and Avery J. Prevalence, incidence and years lived with disability due to polycystic ovary syndrome in 204 countries and territories, 1990-2019. Hum Reprod 2022; 37: 1919-1931.
[6] Wellons MF, Matthews JJ and Kim C. Ovarian aging in women with diabetes: an overview. Maturitas 2017; 96: 109-113.
[7] Zhang J, Xu JH, Qu QQ and Zhong GQ. Risk of cardiovascular and cerebrovascular events in polycystic ovarian syndrome women: a meta-analysis of cohort studies. Front Cardiovasc Med 2020; 7: 552421.
[8] Huhtaniemi I, Hovatta O, La Marca A, Livera G, Monniaux D, Persani L, Heddar A, Jarzabek K, Laisk-Podar T, Salumets A, Tapanainen JS, Veitia RA, Visser JA, Wieacker P, Wolczynski S and Misrahi M. Advances in the molecular pathophysiology, genetics, and treatment of primary ovarian insufficiency. Trends Endocrinol Metab 2018; 29: 400-419.
[9] Ishizuka B. Current understanding of the etiology, symptomatology, and treatment options in premature ovarian insufficiency (POI). Front Endocrinol (Lausanne) 2021; 12: 626924.
[10] Li Z, Chen C, Yu W, Xu L, Jia H, Wang C, Pei N, Liu Z, Luo D, Wang J, Lv W, Yuan B, Zhang J and Jiang H. Colitis-mediated dysbiosis of the intestinal flora and impaired vitamin A absorption reduce ovarian function in mice. Nutrients 2023; 15: 2425.
[11] Kunz C, Kuntz S and Rudloff S. Intestinal flora. Adv Exp Med Biol 2009; 639: 67-79.
[12] Yin L, Yang H, Li J, Li Y, Ding X, Wu G and Yin Y. Pig models on intestinal development and therapeutics. Amino Acids 2017; 49: 2099-2106.
[13] Madan S and Mehra MR. Gut dysbiosis and heart failure: navigating the universe within. Eur J Heart Fail 2020; 22: 629-637.
[14] Sun Q, Cheng L, Zeng X, Zhang X, Wu Z and Weng P. The modulatory effect of plant polysaccharides on gut flora and the implication for neurodegenerative diseases from the perspective of the microbiota-gut-brain axis. Int J Biol Macromol 2020; 164: 1484-1492.
[15] Wang L, Zhou J, Gober HJ, Leung WT, Huang Z, Pan X, Li C, Zhang N and Wang L. Alterations in the intestinal microbiome associated with PCOS affect the clinical phenotype. Biomed Pharmacother 2021; 133: 110958.
[16] Yan J, Kong L, Zhang X, Yu M, Zhu K, Zhao A, Shi D, Sun Y, Wang J, Shen W and Li L. Maternal zearalenone exposure affects gut microbiota and follicular development in suckled offspring. J Agric Food Chem 2022; 70: 15570-15582.
[17] Lüll K, Arffman RK, Sola-Leyva A, Molina NM, Aasmets O, Herzig KH, Plaza-Díaz J, Franks S, Morin-Papunen L, Tapanainen JS, Salumets A, Altmäe S, Piltonen TT and Org E. The gut microbiome in polycystic ovary syndrome and its association with metabolic traits. J Clin Endocrinol Metab 2021; 106: 858-871.
[18] Liu J, Liu Y and Li X. Effects of intestinal flora on polycystic ovary syndrome. Front Endocrinol (Lausanne) 2023; 14: 1151723.
[19] Kim N. Sex difference of gut microbiota. Sex/Gender-Specific Medicine in the Gastrointestinal Diseases 2022; 363-377.
[20] Hamilton KJ, Hewitt SC, Arao Y and Korach KS. Estrogen hormone biology. Curr Top Dev Biol 2017; 125: 109-146.
[21] Nilsson S, Makela S, Treuter E, Tujague M, Thomsen J, Andersson G, Enmark E, Pettersson K, Warner M and Gustafsson JÅ. Mechanisms of estrogen action. Physiol Rev 2001; 81: 1535-1565.
[22] Leung KC, Johannsson G, Leong GM and Ho KK. Estrogen regulation of growth hormone action. Endocr Rev 2004; 25: 693-721.
[23] Sui Y, Wu J and Chen J. The role of gut microbial β-glucuronidase in estrogen reactivation and breast cancer. Front Cell Dev Biol 2021; 9: 631552.
[24] Dabek M, McCrae SI, Stevens VJ, Duncan SH and Louis P. Distribution of β-glucosidase and β-glucuronidase activity and of β-glucuronidase gene gus in human colonic bacteria. FEMS Microbiol Ecol 2008; 66: 487-495.
[25] Guarner-Lans V, Rubio-Ruiz ME, Pérez-Torres I and Baños de MacCarthy G. Relation of aging and sex hormones to metabolic syndrome and cardiovascular disease. Exp Gerontol 2011; 46: 517-523.
[26] Yaffe K, Lui LY, Grady D, Cauley J, Kramer J and Cummings SR. Cognitive decline in women in relation to non-protein-bound oestradiol concentrations. Lancet 2000; 356: 708-712.
[27] d'Afflitto M, Upadhyaya A, Green A and Peiris M. Association between sex hormone levels and gut microbiota composition and diversity-a systematic review. J Clin Gastroenterol 2022; 56: 384-392.
[28] Baker JM, Al-Nakkash L and Herbst-Kralovetz MM. Estrogen-gut microbiome axis: physiological and clinical implications. Maturitas 2017; 103: 45-53.
[29] Flores R, Shi J, Fuhrman B, Xu X, Veenstra TD, Gail MH, Gajer P, Ravel J and Goedert JJ. Fecal microbial determinants of fecal and systemic estrogens and estrogen metabolites: a cross-sectional study. J Transl Med 2012; 10: 253.
[30] Lee JJ, Jung YL, Cheong TC, Espejo Valle-Inclan J, Chu C, Gulhan DC, Ljungström V, Jin H, Viswanadham VV, Watson EV, Cortés-Ciriano I,

Elledge SJ, Chiarle R, Pellman D and Park PJ. ERα-associated translocations underlie oncogene amplifications in breast cancer. Nature 2023; 618: 1024-1032.
[31] Matsushita M, Fujita K, Motooka D, Hatano K, Fukae S, Kawamura N, Tomiyama E, Hayashi Y, Banno E, Takao T, Takada S, Yachida S, Uemura H, Nakamura S and Nonomura N. The gut microbiota associated with high-Gleason prostate cancer. Cancer Sci 2021; 112: 3125-3135.
[32] Wylie K, Rees M, Hackett G, Anderson R, Bouloux PM, Cust M, Goldmeier D, Kell P, Terry T, Trinick T and Wu F. Androgens, health and sexuality in women and men. Maturitas 2010; 67: 275-289.
[33] Basson R, Brotto LA, Petkau AJ and Labrie F. Role of androgens in women's sexual dysfunction. Menopause 2010; 17: 962-971.
[34] Devendran S, Mythen SM and Ridlon JM. The desA and desB genes from Clostridium scindens ATCC 35704 encode steroid-17,20-desmolase. J Lipid Res 2018; 59: 1005-1014.
[35] Sambyal K and Singh RV. Production aspects of testosterone by microbial biotransformation and future prospects. Steroids 2020; 159: 108651.
[36] Colldén H, Landin A, Wallenius V, Elebring E, Fändriks L, Nilsson ME, Ryberg H, Poutanen M, Sjögren K, Vandenput L and Ohlsson C. The gut microbiota is a major regulator of androgen metabolism in intestinal contents. Am J Physiol Endocrinol Metab 2019; 317: E1182-E1192.
[37] Sardana K, Muddebihal A, Sehrawat M, Bansal P and Khurana A. An updated clinico-investigative approach to diagnosis of cutaneous hyperandrogenism in relation to adult female acne, female pattern alopecia & hirsutism a primer for dermatologists. Expert Rev Endocrinol Metab 2024; 19: 111-128.
[38] Gulhan I, Bozkaya G, Uyar I, Oztekin D, Pamuk BO and Dogan E. Serum lipid levels in women with premature ovarian failure. Menopause 2012; 19: 1231-1234.
[39] Neves AR, Montoya-Botero P and Polyzos NP. The role of androgen supplementation in women with diminished ovarian reserve: time to randomize, not meta-analyze. Front Endocrinol (Lausanne) 2021; 12: 653857.
[40] Liu M, Wu K and Wu Y. The emerging role of ferroptosis in female reproductive disorders. Biomed Pharmacother 2023; 166: 115415.
[41] Sherman SB, Sarsour N, Salehi M, Schroering A, Mell B, Joe B and Hill JW. Prenatal androgen exposure causes hypertension and gut microbiota dysbiosis. Gut Microbes 2018; 9: 400-421.
[42] Liang S, Wu X and Jin F. Gut-brain psychology: rethinking psychology from the microbiota-gut-brain axis. Front Integr Neurosci 2018; 12: 33.
[43] Nelson OE and Chukwuma EF. Association of body mass index with hypothalamus-pituitary-ovarian axis hormones in infertile women in the Niger Delta region, Nigeria. Open J Obstet Gynecol 2022; 12: 671-685.
[44] Acevedo-Rodriguez A, Kauffman AS, Cherrington BD, Borges CS, Roepke TA and Laconi M. Emerging insights into hypothalamic-pituitary-gonadal axis regulation and interaction with stress signalling. J Neuroendocrinol 2018; 30: e12590.
[45] Ilie IR. Neurotransmitter, neuropeptide and gut peptide profile in PCOS-pathways contributing to the pathophysiology, food intake and psychiatric manifestations of PCOS. Adv Clin Chem 2020; 96: 85-135.
[46] Wall R, Cryan JF, Ross RP, Fitzgerald GF, Dinan TG and Stanton C. Bacterial neuroactive compounds produced by psychobiotics. Adv Exp Med Biol 2014; 817: 221-239.
[47] Romero-Reyes J, Cárdenas M, Damián-Matsumura P, Domínguez R and Ayala ME. Inhibition of serotonin reuptake in the prepubertal rat ovary by fluoxetine and effects on ovarian functions. Reprod Toxicol 2016; 59: 80-88.
[48] Ruas-Madiedo P, Medrano M, Salazar N, De Los Reyes-Gavilán CG, Pérez PF and Abraham AG. Exopolysaccharides produced by Lactobacillus and Bifidobacterium strains abrogate in vitro the cytotoxic effect of bacterial toxins on eukaryotic cells. J Appl Microbiol 2010; 109: 2079-2086.
[49] Kuebutornye FK, Tang J, Cai J, Yu H, Wang Z, Abarike ED, Lu Y, Li Y and Afriyie G. In vivo assessment of the probiotic potentials of three host-associated Bacillus species on growth performance, health status and disease resistance of Oreochromis niloticus against Streptococcus agalactiae. Aquaculture 2020; 527: 735440.
[50] Haque R, Das II, Sawant PB, Chadha NK, Sahoo L, Kumar R and Sundaray JK. Tenets in microbial endocrinology: a new vista in teleost reproduction. Front Physiol 2022; 13: 871045.
[51] Cai H, Cao X, Qin D, Liu Y, Liu Y, Hua J and Peng S. Gut microbiota supports male reproduction *via* nutrition, immunity, and signaling. Front Microbiol 2022; 13: 977574.
[52] Sullivan Å and Nord CE. The place of probiotics in human intestinal infections. Int J Antimicrob Agents 2002; 20: 313-319.
[53] LeBlanc JG, Chain F, Martín R, Bermúdez-Humarán LG, Courau S and Langella P. Beneficial effects on host energy metabolism of short-chain fatty acids and vitamins produced by commensal and probiotic bacteria. Microb Cell Fact 2017; 16: 79.

[54] Kobyliak N, Conte C, Cammarota G, Haley AP, Styriak I, Gaspar L, Fusek J, Rodrigo L and Kruzliak P. Probiotics in prevention and treatment of obesity: a critical view. Nutr Metab (Lond) 2016; 13: 14.
[55] Zhang B and Guo Y. Supplemental zinc reduced intestinal permeability by enhancing occludin and zonula occludens protein-1 (ZO-1) expression in weaning piglets. Br J Nutr 2009; 102: 687-693.
[56] Scheithauer TP, Dallinga-Thie GM, de Vos WM, Nieuwdorp M and van Raalte DH. Causality of small and large intestinal microbiota in weight regulation and insulin resistance. Mol Metab 2016; 5: 759-770.
[57] He FF and Li YM. Role of gut microbiota in the development of insulin resistance and the mechanism underlying polycystic ovary syndrome: a review. J Ovarian Res 2020; 13: 73.
[58] Xu Y, Zhu Y, Li X and Sun B. Dynamic balancing of intestinal short-chain fatty acids: the crucial role of bacterial metabolism. Trends Food Sci Tech 2020; 100: 118-130.
[59] Drasar BS and Hill MJ. Intestinal bacteria and cancer. The Am J Clin Nutr 1972; 25: 1399-1404.
[60] Wang J, Jia R, Gong H, Celi P, Zhuo Y, Ding X, Bai S, Zeng Q, Yin H, Xu S, Liu J, Mao X and Zhang K. The effect of oxidative stress on the chicken ovary: involvement of microbiota and melatonin interventions. Antioxidants (Basel) 2021; 10: 1422.
[61] Yang YL, Zhou WW, Wu S, Tang WL, Wang ZW, Zhou ZY, Li ZW, Huang QF, He Y and Zhou HW. Intestinal flora is a key factor in insulin resistance and contributes to the development of polycystic ovary syndrome. Endocrinology 2021; 162: bqab118.
[62] Liu M, Yan J, Wu Y, Zhu H, Huang Y and Wu K. The impact of herbal medicine in regulating intestinal flora on female reproductive disorders. Front Pharmacol 2022; 13: 1026141.
[63] Zhao QQ, Ni ZX, Bi YL, Sun S, Cheng W and Yu CQ. Huayu Jiedu prescription alleviates gut microbiota and fecal metabolites in mice with endometriosis. Chinese Journal of Experimental Traditional Medical Formulae 2021; 202-214.
[64] Zehra B and Khursheed A. Polycystic ovarian syndrome: symptoms, treatment and diagnosis: a review. J Pharmacognosy Phytochem 2018; 7: 875-880.
[65] Maachi M, Pieroni L, Bruckert E, Jardel C, Fellahi S, Hainque B, Capeau J and Bastard JP. Systemic low-grade inflammation is related to both circulating and adipose tissue TNFα, leptin and IL-6 levels in obese women. Int J Obes Relat Metab Disord 2004; 28: 993-997.
[66] Sun X, Cui Y, Su Y, Gao Z, Diao X, Li J, Zhu X, Li D, Li Z, Wang C and Shi Y. Dietary fiber ameliorates lipopolysaccharide-induced intestinal barrier function damage in piglets by modulation of intestinal microbiome. mSystems 2021; 6: e01374-20.
[67] Linsalata M, Riezzo G, D'Attoma B, Clemente C, Orlando A and Russo F. Noninvasive biomarkers of gut barrier function identify two subtypes of patients suffering from diarrhoea predominant-IBS: a case-control study. BMC Gastroenterol 2018; 18: 167.
[68] Serek P and Oleksy-Wawrzyniak M. The effect of bacterial infections, probiotics and zonulin on intestinal barrier integrity. Int J Mol Sci 2021; 22: 11359.
[69] Rahman MA, Pal RK, Islam N, Freeman R, Berthiaume F, Mazzeo A and Ashraf A. A facile graphene conductive polymer paper based biosensor for dopamine, TNF-α, and IL-6 detection. Sensors (Basel) 2023; 23: 8115.
[70] Yang T, Li G, Xu Y, He X, Song B and Cao Y. Characterization of the gut microbiota in polycystic ovary syndrome with dyslipidemia. BMC Microbiol 2024; 24: 169.
[71] Tsuzuno T, Takahashi N, Yamada-Hara M, Yokoji-Takeuchi M, Sulijaya B, Aoki-Nonaka Y, Matsugishi A, Katakura K, Tabeta K and Yamazaki K. Ingestion of Porphyromonas gingivalis exacerbates colitis via intestinal epithelial barrier disruption in mice. J Periodontal Res 2021; 56: 275-288.
[72] Guo Y, Qi Y, Yang X, Zhao L, Wen S, Liu Y and Tang L. Association between polycystic ovary syndrome and gut microbiota. PLoS One 2016; 11: e0153196.
[73] Wijeyaratne CN, Balen AH, Barth JH and Belchetz PE. Clinical manifestations and insulin resistance (IR) in polycystic ovary syndrome (PCOS) among South Asians and Caucasians: is there a difference? Clin Endocrinol (Oxf) 2002; 57: 343-350.
[74] Guney C, Bal NB and Akar F. The impact of dietary fructose on gut permeability, microbiota, abdominal adiposity, insulin signaling and reproductive function. Heliyon 2023; 9: e18896.
[75] Kosmalski M, Śliwińska A and Drzewoski J. Non-alcoholic fatty liver disease or type 2 diabetes mellitus-the chicken or the egg dilemma. Biomedicines 2023; 11: 1097.
[76] Li Q, He R, Zhang F, Zhang J, Lian S and Liu H. Combination of oligofructose and metformin alters the gut microbiota and improves metabolic profiles, contributing to the potentiated therapeutic effects on diet-induced obese animals. Front Endocrinol (Lausanne) 2020; 10: 939.
[77] Ni Z, Cheng W, Ding J, Yao R, Zhang D, Zhai D, Zhou L and Yu C. Impact of Buzhong Yiqi prescription on the gut microbiota of patients with obesity manifesting polycystic ovarian syn-

drome. Evid Based Complement Alternat Med 2021; 2021: 6671367.
[78] Wang J, Wu D, Guo H and Li M. Hyperandrogenemia and insulin resistance: the chief culprit of polycystic ovary syndrome. Life Sci 2019; 236: 116940.
[79] DuPont AW and DuPont HL. The intestinal microbiota and chronic disorders of the gut. Nat Rev Gastroenterol Hepatol 2011; 8: 523-531.
[80] Vojnović Milutinović D, Teofilović A, Veličković N, Brkljačić J, Jelača S, Djordjevic A and Macut D. Glucocorticoid signaling and lipid metabolism disturbances in the liver of rats treated with 5α-dihydrotestosterone in an animal model of polycystic ovary syndrome. Endocrine 2021; 72: 562-572.
[81] Wu J, Zhuo Y, Liu Y, Chen Y, Ning Y and Yao J. Association between premature ovarian insufficiency and gut microbiota. BMC Pregnancy Childbirth 2021; 21: 418.
[82] Li M, Zhu Y, Wei J, Chen L, Chen S and Lai D. The global prevalence of premature ovarian insufficiency: a systematic review and meta-analysis. Climacteric 2023; 26: 95-102.
[83] Szeliga A, Calik-Ksepka A, Maciejewska-Jeske M, Grymowicz M, Smolarczyk K, Kostrzak A, Smolarczyk R, Rudnicka E and Meczekalski B. Autoimmune diseases in patients with premature ovarian insufficiency-our current state of knowledge. Int J Mol Sci 2021; 22: 2594.
[84] Domniz N and Meirow D. Premature ovarian insufficiency and autoimmune diseases. Best Pract Res Clin Obstet Gynaecol 2019; 60: 42-55.
[85] Kirshenbaum M and Orvieto R. Premature ovarian insufficiency (POI) and autoimmunity-an update appraisal. J Assist Reprod Genet 2019; 36: 2207-2215.
[86] Purchiaroni F, Tortora A, Gabrielli M, Bertucci F, Gigante G, Ianiro G, Ojetti V, Scarpellini E and Gasbarrini A. The role of intestinal microbiota and the immune system. Eur Rev Med Pharmacol Sci 2013; 17: 323-33.
[87] Jiao X, Zhang X, Li N, Zhang D, Zhao S, Dang Y, Zanvit P, Jin W, Chen ZJ, Chen W and Qin Y. Treg deficiency-mediated TH1 response causes human premature ovarian insufficiency through apoptosis and steroidogenesis dysfunction of granulosa cells. Clin Transl Med 2021; 11: e448.
[88] Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly-Y M, Glickman JN and Garrett WS. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science 2013; 341: 569-573.
[89] Shin SY, Hussain Z, Lee YJ and Park H. An altered composition of fecal microbiota, organic acids, and the effect of probiotics in the guinea pig model of postoperative ileus. Neurogastroenterol Motil 2021; 33: e13966.
[90] Han SJ, Jung SY, Wu SP, Hawkins SM, Park MJ, Kyo S, Qin J, Lydon JP, Tsai SY, Tsai MJ, DeMayo FJ and O'Malley BW. Estrogen receptor β modulates apoptosis complexes and the inflammasome to drive the pathogenesis of endometriosis. Cell 2015; 163: 960-974.
[91] Medina-Perucha L, Pistillo A, Raventós B, Jacques-Aviñó C, Munrós-Feliu J, Martínez-Bueno C, Valls-Llobet C, Carmona F, López-Jiménez T, Pujolar-Díaz G, Flo Arcas E, Berenguera A and Duarte-Salles T. Endometriosis prevalence and incidence trends in a large population-based study in Catalonia (Spain) from 2009 to 2018. Womens Health (Lond) 2022; 18: 17455057221130566.
[92] Begum MIA, Chuan L, Hong ST and Chae HS. The pathological role of miRNAs in endometriosis. Biomedicines 2023; 11: 3087.
[93] Taghavipour M, Sadoughi F, Mirzaei H, Yousefi B, Moazzami B, Chaichian S, Mansournia MA and Asemi Z. Apoptotic functions of microRNAs in pathogenesis, diagnosis, and treatment of endometriosis. Cell Biosci 2020; 10: 12.
[94] Wei Y, Tan H, Yang R, Yang F, Liu D, Huang B, OuYang L, Lei S, Wang Z, Jiang S, Cai H, Xie X, Yao S and Liang Y. Gut dysbiosis-derived β-glucuronidase promotes the development of endometriosis. Fertil Steril 2023; 120: 682-694.
[95] Chadchan SB, Popli P, Ambati CR, Tycksen E, Han SJ, Bulun SE, Putluri N, Biest SW and Kommagani R. Gut microbiota-derived short-chain fatty acids protect against the progression of endometriosis. Life Sci Alliance 2021; 4: e202101224.
[96] Ye Q, Zeng X, Wang S, Zeng X, Yang G, Ye C, Cai S, Chen M, Li S and Qiao S. Butyrate drives the acetylation of histone H3K9 to activate steroidogenesis through PPARγ and PGC1α pathways in ovarian granulosa cells. FASEB J 2021; 35: e21316.
[97] Shan J, Ni Z, Cheng W, Zhou L, Zhai D, Sun S and Yu C. Gut microbiota imbalance and its correlations with hormone and inflammatory factors in patients with stage 3/4 endometriosis. Arch Gynecol Obstet 2021; 304: 1363-1373.
[98] Kim JE, Kim SJ, Jeong HW, Lee BH, Choi JY, Park RW, Park JY and Kim IS. RGD peptides released from βig-h3, a TGF-β-induced cell-adhesive molecule, mediate apoptosis. Oncogene 2003; 22: 2045-2053.
[99] Tsai CE, Chiu CT, Rayner CK, Wu KL, Chiu YC, Hu ML, Chuah SK, Tai WC, Liang CM and Wang HM. Associated factors in Streptococcus bovis bacteremia and colorectal cancer. Kaohsiung J Med Sci 2016; 32: 196-200.

[100] Christodoulakos G, Augoulea A, Lambrinoudaki I, Sioulas V and Creatsas G. Pathogenesis of endometriosis: the role of defective 'immunosurveillance'. Eur J Contracept Reprod Health Care 2007; 12: 194-202.
[101] Vinatier D, Orazi G, Cosson M and Dufour P. Theories of endometriosis. Eur J Obstet Gynecol Reprod Biol 2001; 96: 21-34.
[102] Linskens RK, Huijsdens XW, Savelkoul PH, Vandenbroucke-Grauls CM and Meuwissen SG. The bacterial flora in inflammatory bowel disease: current insights in pathogenesis and the influence of antibiotics and probiotics. Scand J Gastroenterol Suppl 2001; 29-40.
[103] Chen VW, Ruiz B, Killeen JL, Coté TR, Wu XC and Correa CN. Pathology and classification of ovarian tumors. Cancer 2003; 97 Suppl: 2631-2642.
[104] Yada-Hashimoto N, Yamamoto T, Kamiura S, Seino H, Ohira H, Sawai K, Kimura T and Saji F. Metastatic ovarian tumors: a review of 64 cases. Gynecol Oncol 2003; 89: 314-317.
[105] Chase D, Goulder A, Zenhausern F, Monk B and Herbst-Kralovetz M. The vaginal and gastrointestinal microbiomes in gynecologic cancers: a review of applications in etiology, symptoms and treatment. Gynecol Oncol 2015; 138: 190-200.
[106] Houghton LA and Whorwell PJ. Towards a better understanding of abdominal bloating and distension in functional gastrointestinal disorders. Neurogastroenterol Motil 2005; 17: 500-511.
[107] Liu Q, Yang W, Luo N, Liu J, Wu Y, Ding J, Li C and Cheng Z. LPS and IL-8 activated umbilical cord blood-derived neutrophils inhibit the progression of ovarian cancer. J Cancer 2020; 11: 4413-4420.
[108] Zhao Y, Tao F, Jiang J, Chen L, Du J, Cheng X, He Q, Zhong S, Chen W, Wu X, Ou R, Xu Y and Tang KF. Tryptophan 2, 3-dioxygenase promotes proliferation, migration and invasion of ovarian cancer cells. Mol Med Rep 2021; 23: 445.
[109] Ruze R, Song J, Yin X, Chen Y, Xu R, Wang C and Zhao Y. Mechanisms of obesity- and diabetes mellitus-related pancreatic carcinogenesis: a comprehensive and systematic review. Signal Transduct Target Ther 2023; 8: 139.
[110] Yaginuma S, Omi J, Uwamizu A and Aoki J. Emerging roles of lysophosphatidylserine as an immune modulator. Immunol Rev 2023; 317: 20-29.
[111] Pan T, Pei Z, Fang Z, Wang H, Zhu J, Zhang H, Zhao J, Chen W and Lu W. Uncovering the specificity and predictability of tryptophan metabolism in lactic acid bacteria with genomics and metabolomics. Front Cell Infect Microbiol 2023; 13: 1154346.
[112] Xu S, Liu Z, Lv M, Chen Y and Liu Y. Intestinal dysbiosis promotes epithelial-mesenchymal transition by activating tumor-associated macrophages in ovarian cancer. Pathog Dis 2019; 77: ftz019.
[113] Miao R, Badger TC, Groesch K, Diaz-Sylvester PL, Wilson T, Ghareeb A, Martin JA, Cregger M, Welge M, Bushell C, Auvil L, Zhu R, Brard L and Braundmeier-Fleming A. Assessment of peritoneal microbial features and tumor marker levels as potential diagnostic tools for ovarian cancer. PLoS One 2020; 15: e0227707.
[114] Sánchez B, Delgado S, Blanco-Míguez A, Lourenço A, Gueimonde M and Margolles A. Probiotics, gut microbiota, and their influence on host health and disease. Mol Nutr Food Res 2017; 61.
[115] Tegegne BA and Kebede B. Probiotics, their prophylactic and therapeutic applications in human health development: a review of the literature. Heliyon 2022; 8: e09725.
[116] Duan H, Yu L, Tian F, Zhai Q, Fan L and Chen W. Antibiotic-induced gut dysbiosis and barrier disruption and the potential protective strategies. Crit Rev Food Sci Nutr 2022; 62: 1427-1452.
[117] Alvarez-Olmos MI and Oberhelman RA. Probiotic agents and infectious diseases: a modern perspective on a traditional therapy. Clin Infect Dis 2001; 32: 1567-1576.
[118] Wittenberger MD, Hagerman RJ, Sherman SL, McConkie-Rosell A, Welt CK, Rebar RW, Corrigan EC, Simpson JL and Nelson LM. The FMR1 premutation and reproduction. Fertil Steril 2007; 87: 456-465.
[119] Jin P and Xie Y. Treatment strategies for women with polycystic ovary syndrome. Gynecol Endocrinol 2018; 34: 272-277.
[120] Ahmadi S, Jamilian M, Karamali M, Tajabadi-Ebrahimi M, Jafari P, Taghizadeh M, Memarzadeh MR and Asemi Z. Probiotic supplementation and the effects on weight loss, glycaemia and lipid profiles in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Hum Fertil (Camb) 2017; 20: 254-261.
[121] Delzenne NM, Knudsen C, Beaumont M, Rodriguez J, Neyrinck AM and Bindels LB. Contribution of the gut microbiota to the regulation of host metabolism and energy balance: a focus on the gut-liver axis. Proc Nutr Soc 2019; 78: 319-328.
[122] Salles BIM, Cioffi D and Ferreira SRG. Probiotics supplementation and insulin resistance: a systematic review. Diabetol Metab Syndr 2020; 12: 98.
[123] Kang Y, Kang X, Yang H, Liu H, Yang X, Liu Q, Tian H, Xue Y, Ren P, Kuang X, Cai Y, Tong M, Li L and Fan W. Lactobacillus acidophilus ameliorates obesity in mice through modulation of

gut microbiota dysbiosis and intestinal permeability. Pharmacol Res 2022; 175: 106020.
[124] López-Gómez L, Szymaszkiewicz A, Zielińska M and Abalo R. Nutraceuticals and enteric glial cells. Molecules 2021; 26: 3762.
[125] Bordalo Tonucci L, Dos Santos KM, De Luces Fortes Ferreira CL, Ribeiro SM, De Oliveira LL and Martino HS. Gut microbiota and probiotics: focus on diabetes mellitus. Crit Rev Food Sci Nutr 2017; 57: 2296-2309.
[126] Zhu R, Lang T, Yan W, Zhu X, Huang X, Yin Q and Li Y. Gut microbiota: influence on carcinogenesis and modulation strategies by drug delivery systems to improve cancer therapy. Adv Sci (Weinh) 2021; 8: 2003542.
[127] Borella F, Carosso AR, Cosma S, Preti M, Collemi G, Cassoni P, Bertero L and Benedetto C. Gut microbiota and gynecological cancers: a summary of pathogenetic mechanisms and future directions. ACS Infect Dis 2021; 7: 987-1009.
[128] Zeng W, Shen J, Bo T, Peng L, Xu H, Nasser MI, Zhuang Q and Zhao M. Cutting edge: probiotics and fecal microbiota transplantation in immunomodulation. J Immunol Res 2019; 2019: 1603758.
[129] Cheng H, Wang Z, Cui L, Wen Y, Chen X, Gong F and Yi H. Opportunities and challenges of the human microbiome in ovarian cancer. Front Oncol 2020; 10: 163.
[130] Najafi S, Majidpoor J and Mortezaee K. The impact of microbiota on PD-1/PD-L1 inhibitor therapy outcomes: a focus on solid tumors. Life Sci 2022; 310: 121138.
[131] Tymoszuk P, Nairz M, Brigo N, Petzer V, Heeke S, Kircher B, Hermann-Kleiter N, Klepsch V, Theurl I, Weiss G and Pfeifhofer-Obermair C. Iron supplementation interferes with immune therapy of murine mammary carcinoma by inhibiting anti-tumor T cell function. Front Oncol 2020; 10: 584477.
[132] Gao Y, Shang Q, Li W, Guo W, Stojadinovic A, Mannion C, Man YG and Chen T. Antibiotics for cancer treatment: a double-edged sword. J Cancer 2020; 11: 5135-5149.
[133] Li Q, Ma L, Shen S, Guo Y, Cao Q, Cai X, Feng J, Yan Y, Hu T, Luo S, Zhou L, Peng B, Yang Z and Hua Y. Intestinal dysbacteriosis-induced IL-25 promotes development of HCC via alternative activation of macrophages in tumor microenvironment. J Exp Clin Cancer Res 2019; 38: 303.