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## EDITED BY

Bo Liu,  
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China

## REVIEWED BY

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Harbin Medical University, China  
Ershun Zhou,  
Foshan University, China  
Jie Chen,  
Sichuan University, China

## \*CORRESPONDENCE

Weiliang Zhao  
✉ zhaoweil@jlu.edu.cn

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# Gut microbiota dysbiosis in polycystic ovary syndrome: Mechanisms of progression and clinical applications

Yan Sun<sup>1</sup>, Shouyang Gao<sup>2</sup>, Cong Ye<sup>2</sup> and Weiliang Zhao<sup>1\*</sup>

<sup>1</sup>Department of Anesthesiology, China-Japan Union Hospital of Jilin University, Changchun, Jilin, China, <sup>2</sup>Department of Obstetrics and Gynecology, China-Japan Union Hospital of Jilin University, Changchun, Jilin, China

Polycystic ovary syndrome (PCOS) is the most common endocrine diseases in women of childbearing age that leads to menstrual disorders and infertility. The pathogenesis of PCOS is complex and has not yet been fully clarified. Gut microbiota is associated with disorders of lipid, glucose, and steroid hormone metabolism. A large body of studies demonstrated that gut microbiota could regulate the synthesis and secretion of insulin, and affect androgen metabolism and follicle development, providing us a novel idea for unravelling the pathogenesis of PCOS. The relationship between gut microbiota and the pathogenesis of PCOS is particularly important. This study reviewed recent research advances in the roles of gut microbiota in the occurrence and development of PCOS. It is expected to provide a new direction for the treatment of PCOS based on gut microbiota.

## KEYWORDS

Polycystic ovary syndrome, gut microbiota, insulin, infertility, women

## Introduction

PCOS is the most common endocrine diseases with complex etiology and pathogenesis (Glntborg and Andersen, 2010). Among women of childbearing age, the prevalence of PCOS is as high as 5%~10%. It accounts for 50%~70% of anovulatory infertility (Sirmans and Pate, 2013). PCOS is mainly characterized by excessive androgen secretion, ovulation disorders and polycystic ovarian changes, and can be accompanied by abdominal obesity, insulin resistance, impaired glucose metabolism and dyslipidemia (Froment et al., 2022). Its short-term complications include infertility, abortion, preterm delivery and other adverse pregnancy outcomes, which can increase the risk of diabetes, coronary heart disease, endometrial cancer and other diseases in the long term (Hirschberg, 2009). At present, most scholars believe that PCOS is a disease that is controlled by multiple genes and induced by multiple factors. The pathogenesis of PCOS is still unclear, and the clinical treatment effect of many patients is poor.

There are abundant microorganisms in the human intestine. Gut microbiota and the host live together for life and are mutually beneficial. It has become a research hotspot in cancer, immune diseases and metabolic diseases (Hu et al., 2020; Zhao CJ. et al., 2022; Zhao MK. et al., 2022). In recent years, there are also some research reports on the gut microbiota of PCOS patients and its relationship with metabolic abnormalities (Siddiqui et al., 2022). Studies have shown that the gut microbiota of PCOS patients is related to the occurrence and development of insulin resistance, hyperandrogenism, chronic inflammation and metabolic syndrome, and may affect the clinical manifestations of PCOS through short chain fatty acids, lipopolysaccharide, sex hormones and brain-gut axis (Gu et al., 2022; Zhang et al., 2022). In addition, a number of clinical studies have attempted to use fecal microbiota transplantation, probiotics supplementation and traditional Chinese medicine to regulate gut microbiota and explore the possibility of treating certain diseases (Quaranta et al., 2019).

## Changes of gut microbiota composition in PCOS

The composition of human gut microbiota is complex. More and more studies have shown that gut microbiota is closely related to glucose and lipid metabolism (Roessler et al., 2022). Compared with normal people, the composition of gut microbiota in obese, type 2 diabetes and other people changes, and their different flora may participate in inflammatory response, affect the stability of intestinal barrier and improve metabolism (Moser et al., 2022; Sugawara et al., 2022). At present, the pathogenesis of PCOS is still unclear. Many studies have shown that gut microbiota played an important role in PCOS occurrence and development (Duan et al., 2021). A previous study found that decreased intestinal bacteria *Bacteroides*, and increased *Firmicis* and *Proteus* were observed in mice of dehydroepiandrosterone/high-fat diet induced PCOS. Correlation analysis showed that the level of inflammatory factors in mice was correlated with the abundance of gut microbiota (Lin et al., 2021). Compared with the healthy control group, letrozole induced PCOS rats had less intestinal lactobacillus, rumen coccus, and clostridium, and more pullorum (Zhao HY. et al., 2022). Compared with healthy people, the gut microbial diversity of PCOS patients decreased, the composition changed, and the intestinal mucosal barrier was damaged (Lindheim et al., 2017). Compared with non-obese PCOS patients and healthy control population, obese PCOS patients have increased enterobacteria, decreased lactobacillus and bifidobacteria, and changes in gut microbiota are related to inflammation level and insulin resistance (Zhou et al., 2020). Zeng et al. pointed out that there were differences in the composition and structure of gut microbiota in PCOS patients with or without insulin resistance (Zeng et al., 2019). These studies showed that the diversity of gut microbiota and the abundance of related flora in patients with PCOS changed. The gut microbiota

may change the stability of intestinal mucosa and then affect its metabolism by participating in the occurrence of inflammatory reaction in patients with PCOS (Zeng et al., 2019).

## Gut microbiota and the pathological mechanism of PCOS

Gut microbiota is the “endocrine organ” to maintain human health. Gut microbiota affects the reproductive endocrine system by interacting with estrogen, androgen, insulin, etc (Qi et al., 2021). The typical characteristics of PCOS include abnormal levels of sex hormones, insulin resistance, polycystic changes in the ovary, chronic subclinical inflammation, etc (Szukiewicz et al., 2022). The gut microbiota disorder is involved in endotoxemia, SCFA production, bile acid metabolism, abnormal secretion of brain gut peptides, etc. The above physiological and pathological processes are related to the manifestations of PCOS such as hyperandrogenism, insulin resistance, chronic inflammatory reaction, abnormal levels of brain gut peptide (Li MW. et al., 2022). Therefore, gut microbiota may affect follicular development, sex hormones and metabolic levels through hyperandrogenism, insulin resistance, chronic inflammation, brain-gut axis, etc., and participate in the pathogenesis of PCOS.

## Gut microbiota and insulin resistance

Insulin resistance is one of the most common endocrine characteristics in PCOS patients (Petrillo et al., 2022). 50%~70% of PCOS patients have insulin resistance of different degrees, especially in obese patients. The risk of diabetes in PCOS patients is higher than that in normal women. Insulin resistance and obesity can aggravate the disorder of glucose and lipid metabolism and hyperandrogenin blood in patients with PCOS (Amisi, 2022). Studies have shown that increasing dietary fiber intake and oral butyrate supplements can prevent obesity and improve insulin sensitivity (Mayorga-Ramos et al., 2022). The imbalance of gut microbiota can change the content of SCFAs, especially in PCOS patients with insulin resistance.

Studies have shown that the occurrence of insulin resistance is closely related to gut microbiota disorder (Martinez-Montoro et al., 2022). Zeng et al. compared the gut microbiota of PCOS patients with insulin resistance with that of the healthy control group, and found that the abundance of *Prevotella* decreased and *Bacteroides* increased in the former group (Zeng et al., 2019). Gut microbiota may affect bile acid metabolism and lead to insulin resistance. Studies showed that the common *Bacteroides* in intestinal microorganisms of PCOS patients increased significantly, which may be caused by the reduction of IL-22, insulin resistance and finally PCOS by affecting the level of bile acid synthesis (Qi X. et al., 2019; Qi et al., 2020).

## Gut microbiota and hyperandrogenism

Hyperandrogenism plays an important pathophysiological role in the pathogenesis of PCOS (Witchel et al., 2022). The common clinical manifestations are hirsutism and acne. Studies have shown that hyperandrogenism are related to gut microbiota (Torres et al., 2019). Zhang et al. found that PCOS mice induced by dihydrotestosterone had an increase in the number of chlamydia, but a decrease in the number of *Escherichia coli*, and affected body mass and fat mass, suggesting that gut microbiota was related to the level of hyperandrogenin in mice (Zhang et al., 2019). Chu et al. found that after transplanting the gut microbiota of male mice to female mice, the basal metabolism of the latter was abnormal, and the testosterone level of mice in the bacterial environment was higher than that of mice in the sterile environment. This indicates that intestinal microbes affect the secretion of testosterone in the body. Markle et al. showed that hyperandrogenism may cause insulin resistance and metabolic abnormalities of PCOS by causing intestinal bacteria enrichment (Markle, 2001). Kelley et al. found the diversity of gut microbiota decreased in Trazole induced Kaohsiung PCOS mouse model (Kelley et al., 2016). Barroso et al. found that the gut microbiota diversity of female rats exposed to a high androgen level environment within 24 hours after birth was reduced, and the risk of metabolic disease in adult offspring was increased, which indicated that the early androgen exposure of female offspring with PCOS might lead to long-term changes in their gut microbiota and metabolic function (Barroso et al., 2020).

## Gut microbiota and chronic inflammation

Leaky gut refers to the dysfunction of the intestinal barrier and has been reported to be related to many diseases. The disorder of gut microbiota could lead to leaky gut. *Bacteroides* and *Escherichia coli* in human intestine belong to *Gram-negative* bacteria. LPS is an important component of the cell wall of *Gram-negative* bacteria. Increased LPS absorption from leaky gut has been suggested by several studies. After intestinal mucosal injury, LPS enters the circulation and forms endotoxemia. Through LPS binding protein (LBP), CD14 and bone marrow differentiation factor-2 (MD-2), LPS is recognized and bound by TLR4 (Page et al., 2022). LPS could induce the expression of inflammatory cytokines and inflammatory mediators. The expression of inflammatory factors such as interleukin 6 (IL-6) and interleukin 6 (IL-6) can activate the inflammatory response. Insulin resistance is considered to be the core of metabolic abnormalities in PCOS patients, which promotes the chronic inflammatory state of PCOS patients (Dahan et al., 2022). It has been studied that mice in the two groups were fed with normal and high-fat diets respectively. After 4 weeks, mice fed with high-fat diet became obese and showed signs of insulin resistance. The LPS concentration in blood of mice in the high-fat diet group was 2-3 times higher than that of the control group. LPS was subcutaneously injected into mice in the control group fed with

normal diet. After 4 weeks, mice in the control group became obese and produced insulin resistance (Fang et al., 2022).

PCOS patients exhibit chronic inflammatory state (Escobar-Morreale et al., 2011). Macrophages are one of the cells involved in inflammation regulation. A large number of macrophages can be seen infiltrating in ovarian tissue of PCOS patients (Tedesco et al., 2019). In addition, major inflammatory factors in peripheral blood of PCOS patients, such as TNF- $\alpha$ , C-reactive protein, IL-1, IL-6 increased in varying degrees. Other studies have shown that the number of T helper cells in PCOS patients is higher than that in normal women (Yang et al., 2021). Under the stimulation of inflammatory factors such as IL-6, T helper cells 17 can secrete proinflammatory factors, induce the inflammatory state of the body, and lead to adverse outcomes of hyperandrogenism, insulin resistance, and ovulation disorders (Nasri et al., 2018). *Wadsworthia* in the family *Bifidobacteriaceae* is a pathogen related to the prophase of inflammatory response, and closely related to the formation of a variety of inflammatory diseases (Burrichter et al., 2021). The gut microbiota of sterile mice transplanted with fecal bacteria from PCOS patients was detected by 16s rDNA sequencing technology. It was found that the level of *wadsworthia* in mice transplanted with fecal bacteria from PCOS patients was higher than that in mice transplanted with healthy fecal bacteria, suggesting that *wadsworthia* may participate in the pathogenesis of PCOS through the inflammatory process. Qi et al. found that the abundance of *B. vulgatus* in the intestine of PCOS patients increased, the level of bile acid, tauroursodeoxycholic acid and glycodeoxycholic acid, metabolites of intestinal bacteria, decreased, and the level of intestinal immune factor IL-22 also decreased (Qi XY. et al., 2019). It is suggested that the mechanism of IL-22 improving PCOS insulin resistance and ovarian function may be related to inhibiting the inflammatory response of ovarian granulosa cells.

## Brain-gut axis and PCOS

The brain-gut axis is an information exchange system between the brain and the intestine (Hosie et al., 2022). It is a neuroendocrine immune network formed by the central nervous system, the intestinal nervous system, the hypothalamus pituitary adrenal axis and the intestine. The abnormal metabolism of gut microbiota will lead to abnormal secretion of intestinal endopeptides, cytokines and inflammatory factors (Begum et al., 2022). Various gastrointestinal hormones interact with the brain-gut axis (Yin et al., 2022). Studies showed that the secretion of gastrointestinal hormones in PCOS patients is disordered, and the level of GLP-1 is lower than normal (Bednarz et al., 2022). It can delay gastric emptying, regulate appetite, reduce body mass, and promote pancreatic islets  $\beta$  cell proliferation and stimulation of insulin secretion play an important role in a variety of functions (Cena et al., 2020). Therefore, the brain-gut axis may be a new target for insulin resistance therapy in PCOS patients in the future.

The pathological mechanism of PCOS is not only limited to the dysfunction of the hypothalamus pituitary ovary axis, but also involves the brain-gut axis (Liang et al., 2021). The brain-gut axis

is a biphasic signal transduction pathway. The gut and brain are closely connected through the gut brain axis. The brain-gut axis plays an important role in the information exchange system (Li et al., 2023). There is a complex two-way communication system between the central nervous system and the gastrointestinal system (Xu et al., 2022). The microbiota can affect the brain-gut axis in a variety of ways. The gut microbiota can directly stimulate the vagus nerve pathway to send signals to the brain. Various complex information in the intestinal tract can be transmitted to the brain through the synapses formed by the myenteric plexus of the efferent nerve endings and the postganglionic neurons (Wang et al., 2023). At the same time, the gut microbiota forms feedback to the brain by synthesizing hormones and neurotransmitters. For example, the intestinal peptide in the systemic circulation can bind to the homologous receptors of immune cells and the end of the vagus nerve, thus completing the intestinal brain communication (Tan et al., 2022). Gut microbiota disorder may participate in the progress of PCOS through the gut-brain axis (Zhao et al., 2020). Intestinal bacteria can produce SCFA, which is involved in the secretion of brain gut peptides by intestinal endocrine cells, such as glucagon like peptide 1, growth hormone releasing peptide (Ghrelin) and YY peptide. SCFA activates mammalian rapamycin target protein/signal transduction and transcriptional activator signal pathway through G-protein coupled receptor 43 and regulates the expression of brain gut peptide (Zuo et al., 2022). Brain gut peptide (such as Ghrelin) can participate in regulating hypothalamic regulatory nucleus and luteinizing hormone secretion. Ghrelin can also inhibit the excessive synthesis and release of luteinizing hormone by delaying the pulse intensity of pituitary releasing luteinizing hormone, thus participating in regulating the reproductive system function of PCOS (Hoover et al., 2021).

## Treatment of PCOS based on gut microbiome

### Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is a new treatment for inflammatory bowel disease. FMT is now widely believed to be the transplantation of feces from healthy individuals to the intestinal tract of patients, so as to achieve the purpose of treating diseases by improving and rebuilding the gut microbiota (Hamamah et al., 2022). A previous study demonstrated that the transplantation of fecal flora of healthy mice and *Lactobacillus* could improve the gut microbiota structure and restore emotional cycle in letrozole induced PCOS rats (Guo et al., 2016). The PCOS mice exposed to healthy intestinal microbes had improved hormone and glucose and lipid metabolism, decreased testosterone, luteinizing hormone, fasting blood glucose and insulin levels, and improved insulin resistance. Regulation of gut microbiota to improve the metabolism of PCOS may be one of the potential options for future treatment of PCOS, but the specific mechanism remains to be explored in depth (Corrie et al., 2021).

### Herbal medicine

In recent years, it has become a new research hotspot to find active ingredients or prescriptions for treating PCOS from herbal medicine, targeting gut microbiota. Meanwhile, Chinese herbal formulas and active ingredients have been used for the treatment of PCOS for a long time (Li J. et al., 2022). And these herbal medicines and their ingredients have the ability to regulate gut microbiota. A previous study demonstrated that Banxia Xiexin Decoction could attenuate PCOS through regulating gut microbiota (Zhao HY. et al., 2022). Furthermore, it has been reported that Guizhi Fuling Wan could inhibit insulin sensitivity in rat model of PCOS by regulating gut microbiota (Zhu et al., 2020; Liu et al., 2021). In addition, berberine has the ability to attenuate PCOS by regulating gut microbiota (Shen et al., 2021). A previous study also demonstrated that quercetin is considered as a potential agent to attenuate PCOS (Vaez et al., 2022). A large number of studies have confirmed that the disorder of gut microbiota may affect the occurrence and development of PCOS (Yu et al., 2022). Therefore, single Chinese medicine and compound medicine targeting gut microbiota provide new targets for the intervention and treatment of metabolic diseases such as obesity, insulin resistance, diabetes, and provide new research directions for the clinical diagnosis and treatment of PCOS.

### Probiotics and prebiotics

In recent years, with the continuous understanding of gut microbiota, the use of microbial agents in the treatment of PCOS has attracted extensive attention (Zhao et al., 2021). More and more evidences show that probiotics, prebiotics, and synbiotics are effective treatment options for PCOS patients (Miao et al., 2021). The study shows that probiotics can restore the gut microbiota diversity of PCOS mice, improve the flora disorder, and improve the reproductive function of mice (Li T. et al., 2022). On the other hand, based on human studies, 60 PCOS patients were randomly divided into two groups and received probiotic supplementation (bifidobacteria, lactic acid bacteria, etc.) and placebo control tests. After 12 weeks, it was found that the sexual hormone binding protein in the test group was increased, the hirsutism score was reduced by R, insulin sensitivity was increased, and the lipoprotein was reduced, indicating that the intervention treatment of probiotics had a certain effect on PCOS patients. In the diet-induced model of diabetes and obese mice, *B. lactis* B420 strain has been proved to help improve insulin resistance and reduce fat content (Yde et al., 2021). It has been found in clinical studies that the use of *B. lactis* can improve the sex hormone level of PCOS patients. Probiotics may become an important method to intervene in PCOS obesity in the future. In the traditional correlation studies, the relationship between gut microbiota and disease was studied from a macro perspective. In recent years, in some studies on gut microbiota, by identifying different strains and conducting refined research at the level of specific strains, this kind of research method deserves attention.

## Other drugs

Metformin is one of the commonly used drugs for the treatment of PCOS (Ravn et al., 2022). Diane 35 combined with metformin in the treatment of PCOS is more effective than Diane 35 alone in reducing the level of sex hormones and insulin resistance, improving ovulation, increasing pregnancy rate and the total effective rate of treatment, which suggests that metformin plays an important role in the treatment of PCOS (Zhang et al., 2020). Metformin can reduce the level of inflammation in PCOS patients while improving metabolism (Xue et al., 2019). The effect of metformin on gut microbiota has been gradually recognized in recent years (Wu et al., 2022). The research showed that the composition of gut microbiota of newly treated diabetes patients can be changed. After 4 months of treatment with metformin, the gut microbiota of patients was transplanted into sterile hyperglycemic mice, and the glucose tolerance level of mice was improved, suggesting that metformin can achieve therapeutic effect by changing the gut microbiota (Huang et al., 2022). Metformin intervention can improve the metabolic disorder of obese rats, increase the abundance of *Achmania mucophila* and *Clostridium mucosum*, and a total of 18 metabolic pathways (including sphingolipid and fatty acid metabolic pathways) are significantly up-regulated in the gut microbiota. After treatment with metformin, the abundance of *Achmania mucophila* and gut microbiota producing short chain fatty acids, such as bifidobacteria and *Vibrio butyricus*, increased in diabetes patients. When metformin is used in healthy people, the diversity of gut microbiota decreases, and some opportunistic pathogens increase, which may be the reason why metformin causes gastrointestinal side effects (Zhang and Hu, 2020). Research showed that after metformin intervention in PCOS mice, intestinal bacteroides and bifidobacteria increase, proteus, helicobacter and parabacilli decrease, and the level of inflammation in the body improves. Correlation analysis shows that changes in gut microbiota are related to inflammatory factors.

Thiazolidinediones are insulin sensitizers, which can be used together when metformin is not effective. The combination of Diane-35 and pioglitazone can significantly improve the hormone level, fasting blood glucose level, insulin level and blood lipid related indicators in patients with PCOS (Cao et al., 2021). Research shows that pioglitazone can reduce the level of inflammation in patients with PCOS, and the combination of pioglitazone and metformin has a more significant effect (Ali et al., 2019). There are few studies on the relationship between thiazolidinediones and the gut microbiota of PCOS patients. Li et al. found that pioglitazone reduced the intestinal microbial diversity of type 2 diabetes mice (Li et al., 2017).

Although the lipid-lowering drugs are not used as the first-line drugs for PCOS, the regulation of blood lipids is still poor after active intervention, and statins should be considered. The study showed that the androgen level in PCOS patients decreased after long-term use of simvastatin, and the blood lipid metabolism improved significantly (Artar et al., 2022). Atorvastatin can improve the hormone level and insulin resistance of obese PCOS

patients, and improve their inflammatory level *in vivo* (Chen and Zheng, 2021). However, some scholars pointed out that atorvastatin can reduce insulin sensitivity, and statins should be used cautiously (Sabapathy et al., 2022). Lipid regulating drugs can affect the structure of gut microbiota. The study showed that after atorvastatin intervention in hypercholesterolemic rats, the gut microbiota diversity increased. After taking atorvastatin, the abundance of intestinal proteus bacteria in patients with hyperlipidemia is reduced compared with that in patients without atorvastatin, and the abundance of inflammatory related bacteria is reduced, indicating that statins can improve the gut microbiota composition of patients with hyperlipidemia (Khan et al., 2018).

## Conclusions

In conclusion, there are complex and close interactions between PCOS and gut microbiota. The relationship between gut microbiota and the pathogenesis and pathophysiological process of PCOS needs further study. We hope to clarify the relationship between gut microbiota and PCOS by analyzing the metabolites of gut microbiota in patients with PCOS, which provides a new idea for the prevention and treatment of PCOS and metabolic diseases based on gut microbiota.

## Author contributions

YS, SG and WZ wrote the manuscript. WZ revised the review. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## References

- Ali, D. E. S., Shah, M., Ali, A., Malik, M. O., Rehman, F., Badshah, H., et al. (2019). Treatment with metformin and combination of metformin plus pioglitazone on serum levels of IL-6 and IL-8 in polycystic ovary syndrome: A randomized clinical trial. *Hormone. Metab. Res.* 51, 714–722. doi: 10.1055/a-1018-9606
- Amisi, C. A. (2022). Markers of insulin resistance in polycystic ovary syndrome women: An update. *World J. Diabetes* 13, 129–149. doi: 10.4239/wjcd.v13.i3.129
- Artar, G., Tas, B., Turan, G., and Uckan, H. H. (2022). Evaluation of androgen-dependent skin findings of polycystic ovary syndrome (PCOS). *Gynecol. Endocrinol.* 1–5. doi: 10.1080/09513590.2022.2162496
- Barroso, A., Santos-Marcos, J. A., Perdices-Lopez, C., Vega-Rojas, A., Sanchez-Garrido, M. A., Krylova, Y., et al. (2020). Neonatal exposure to androgens dynamically alters gut microbiota architecture. *J. Endocrinol.* 247, 69–85. doi: 10.1530/JOE-20-0277
- Bednarz, K., Kowalczyk, K., Cwynar, M., Czaplak, D., Czarkowski, W., Kmita, D., et al. (2022). The role of glp-1 receptor agonists in insulin resistance with concomitant obesity treatment in polycystic ovary syndrome. *Int. J. Mol. Sci.* 23, 4334. doi: 10.3390/ijms23084334
- Begum, N., Mandhare, A., Tryphena, K. P., Srivastava, S., Shaikh, M. F., Singh, S. B., et al. (2022). Epigenetics in depression and gut-brain axis: A molecular crosstalk. *Front. Aging Neurosci.* 14, 1048333. doi: 10.3389/fnagi.2022.1048333
- Burrichter, A. G., Dorr, S., Bergmann, P., Haiss, S., Keller, A., Fournier, C., et al. (2021). Bacterial microcompartments for isethionate desulfonation in the taurine-degrading human-gut bacterium *Bifidobacterium wadsworthia*. *BMC Microbiol.* 21, 340. doi: 10.1186/s12866-021-02386-w
- Cao, C. J., Qi, Y. Y., Fang, D. M., and Yu, Y. (2021). Clinical study on polycystic ovary syndrome treated with Diane-35 and pioglitazone. *Am. J. Transl. Res.* 13, 12742–12749.
- Cena, H., Chiovato, L., and Nappi, R. E. (2020). Obesity, polycystic ovary syndrome, and infertility: A new avenue for GLP-1 receptor agonists. *J. Clin. Endocrinol. Metab.* 105, e2695–e2709. doi: 10.1210/clinem/dgaa285
- Chen, L. L., and Zheng, J. H. (2021). Effects of atorvastatin on the insulin resistance in women of polycystic ovary syndrome: A systematic review and meta-analysis. *Med. (Baltimore)*. 100, e26289. doi: 10.1097/MD.00000000000026289
- Corrie, L., Gulati, M., Vishwas, S., Kapoor, B., Singh, S. K., Awasthi, A., et al. (2021). Combination therapy of curcumin and fecal microbiota transplant: Potential treatment of polycystic ovarian syndrome. *Med. Hypotheses* 154, 110644. doi: 10.1016/j.mehy.2021.110644
- Dahan, T., Nassar, S., Yajuk, O., Steinberg, E., Benny, O., Abudi, N., et al. (2022). Chronic intermittent hypoxia during sleep causes browning of interscapular adipose tissue accompanied by local insulin resistance in mice. *Int. J. Mol. Sci.* 23, 15462. doi: 10.3390/ijms232415462
- Duan, L. Y., An, X. D., Zhang, Y. H., Jin, D., Zhao, S. H., Zhou, R. R., et al. (2021). Gut microbiota as the critical correlation of polycystic ovary syndrome and type 2 diabetes mellitus. *BioMed. Pharmacother.* 142, 112094. doi: 10.1016/j.biopha.2021.112094
- Escobar-Morreale, H. F., Luque-Ramirez, M., and Gonzalez, F. (2011). Circulating inflammatory markers in polycystic ovary syndrome: A systematic review and metaanalysis. *Fertil. Steril.* 95, 1048–U249. doi: 10.1016/j.fertnstert.2010.11.036
- Fang, J. M., Zeng, L. R., He, Y. L., Liu, X., Zhang, T. C., and Wang, Q. (2022). Effects of dietary tannic acid on obesity and gut microbiota in C57BL/6J mice fed with high-fat diet. *Foods* 11, 3325. doi: 10.3390/foods11213325
- Froment, P., Plotton, I., Giulivi, C., Fabre, S., Khoueiry, R., Mourad, N. I., et al. (2022). At The crossroads of fertility and metabolism: The importance of AMPK-dependent signaling in female infertility associated with hyperandrogenism. *Hum. Reprod.* 37, 1207–1228. doi: 10.1093/humrep/deac067
- Glintborg, D., and Andersen, M. (2010). An update on the pathogenesis, inflammation, and metabolism in hirsutism and polycystic ovary syndrome. *Gynecol. Endocrinol.* 26, 281–296. doi: 10.3109/09513590903247873
- Gu, Y. Y., Zhou, G. N., Zhou, F. Y., Li, Y., Wu, Q. W., He, H. Y., et al. (2022). Gut and vaginal microbiomes in PCOS: Implications for women's health. *Front. Endocrinol.* 13. doi: 10.3389/fendo.2022.808508
- Guo, Y. J., Qi, Y., Yang, X. F., Zhao, L. H., Wen, S., Liu, Y. H., et al. (2016). Association between polycystic ovary syndrome and gut microbiota. *PLoS One* 11, e0153196. doi: 10.1371/journal.pone.0153196
- Hamamah, S., Gheorghita, R., Lobiuc, A., Sirbu, I. O., and Covasa, M. (2022). Fecal microbiota transplantation in non-communicable diseases: Recent advances and protocols. *Front. Med. (Lausanne)*. 9, 1060581. doi: 10.3389/fmed.2022.1060581
- Hirschberg, A. L. (2009). Polycystic ovary syndrome, obesity and reproductive implications. *Womens Health (Lond)*. 5, 529–40; quiz 541–2. doi: 10.2217/WHE.09.39
- Hoover, S. E., Gower, B. A., Cedillo, Y. E., Chandler-Laney, P. C., Deemer, S. E., and Goss, A. M. (2021). Changes in ghrelin and glucagon following a low glycemic load diet in women with PCOS. *J. Clin. Endocrinol. Metab.* 106, e2151–e2161. doi: 10.1210/clinem/dgab028
- Hosie, S., Abo-Shaban, T., Lee, C. Y. Q., Matta, S. M., Shindler, A., Gore, R., et al. (2022). The emerging role of the gut-Brain-Microbiota axis in neurodevelopmental disorders. *Adv. Exp. Med. Biol.* 1383, 141–156. doi: 10.1007/978-3-031-05843-1\_14
- Hu, X., Guo, J., Zhao, C., Jiang, P., Maimai, T., Yanyi, L., et al. (2020). The gut microbiota contributes to the development of staphylococcus aureus-induced mastitis in mice. *Isme. J.* 14, 1897–1910. doi: 10.1038/s41396-020-0651-1
- Huang, Y. X., Lou, X. D., Jiang, C. P., Ji, X. Y., Tao, X. M., Sun, J., et al. (2022). Gut microbiota is correlated with gastrointestinal adverse events of metformin in patients with type 2 diabetes. *Front. Endocrinol.* 13. doi: 10.3389/fendo.2022.1044030
- Kelley, S. T., Skarra, D. V., Rivera, A. J., and Thackray, V. G. (2016). The gut microbiome is altered in a letrozole-induced mouse model of polycystic ovary syndrome. *PLoS One* 11, e0146509. doi: 10.1371/journal.pone.0146509
- Khan, T. J., Ahmed, Y. M., Zamzami, M. A., Mohamed, S. A., Khan, I., Baothman, O. A. S., et al. (2018). Effect of atorvastatin on the gut microbiota of high fat diet-induced hypercholesterolemic rats. *Sci. Rep-Uk*. 8, 662. doi: 10.1038/s41598-017-19013-2
- Li, J., Zheng, R. Q., Lin, Z. X., Hu, F. Y., Lin, Y., Zeng, G. M., et al. (2022). Impact of Chinese herbal medicine on glucolipid metabolic outcomes in women with polycystic ovary syndrome: A systematic review and meta-analysis. *Evid-Based. Compl. Alt.* 2022, 3245663. doi: 10.1155/2022/3245663
- Li, M. W., Chi, X. W., Wang, Y., Setrerrahmane, S., Xie, W. W., and Xu, H. M. (2022). Trends in insulin resistance: insights into mechanisms and therapeutic strategy. *Signal Transduct. Tar.* 7, 216. doi: 10.1038/s41392-022-01073-0
- Li, T., Zhang, Y., Song, J., Chen, L., Du, M., and Mao, X. (2022). Yogurt enriched with inulin ameliorated reproductive functions and regulated gut microbiota in dehydroepiandrosterone-induced polycystic ovary syndrome mice. *Nutrients* 14, 279. doi: 10.3390/nu14020279
- Li, X., Wang, E., Yin, B., Fang, D., Chen, P., Wang, G., et al. (2017). Effects of lactobacillus casei CCFM419 on insulin resistance and gut microbiota in type 2 diabetic mice. *Benef. Microbes* 8, 421–432. doi: 10.3920/BM2016.0167
- Li, Z. H., Jiang, Y. Y., Long, C. Y., Peng, Q., and Yue, R. S. (2023). The gut microbiota-astrocyte axis: Implications for type 2 diabetic cognitive dysfunction. *CNS Neurosci. Ther.* doi: 10.1111/cns.14077
- Liang, Z., Di, N., Li, L., and Yang, D. (2021). Gut microbiota alterations reveal potential gut-brain axis changes in polycystic ovary syndrome. *J. Endocrinol. Invest.* 44, 1727–1737. doi: 10.1007/s40618-020-01481-5
- Lin, W., Wen, L. Y., Wen, J. P., and Xiang, G. D. (2021). Effects of sleeve gastrectomy on fecal gut microbiota and short-chain fatty acid content in a rat model of polycystic ovary syndrome. *Front. Endocrinol.* 12. doi: 10.3389/fendo.2021.747888
- Lindheim, L., Bashir, M., Munzker, J., Trummer, C., Zachhuber, V., Leber, B., et al. (2017). Alterations in gut microbiome composition and barrier function are associated with reproductive and metabolic defects in women with polycystic ovary syndrome (PCOS): A pilot study. *PLoS One* 12, e0168390. doi: 10.1371/journal.pone.0168390
- Liu, M., Zhu, H. Q., Zhu, Y., and Hu, X. D. (2021). Guizhi fuling wan reduces autophagy of granulosa cell in rats with polycystic ovary syndrome via restoring the PI3K/AKT/mTOR signaling pathway. *J. Ethnopharmacol.* 270, 113821. doi: 10.1016/j.jep.2021.113821
- Markle, M. E. (2001). Polycystic ovary syndrome: implications for the advanced practice nurse in primary care. *J. Am. Acad. Nurse. Pract.* 13, 160–163. doi: 10.1111/j.1745-7599.2001.tb00240.x
- Martinez-Montoro, J. I., Damas-Fuentes, M., Fernandez-Garcia, J. C., and Tinahones, F. J. (2022). Role of the gut microbiome in beta cell and adipose tissue crosstalk: A review. *Front. Endocrinol.* 13. doi: 10.3389/fendo.2022.869951
- Mayorga-Ramos, A., Barba-Ostria, C., Simancas-Racines, D., and Guaman, L. P. (2022). Protective role of butyrate in obesity and diabetes: New insights. *Front. Nutr.* 9. doi: 10.3389/fnut.2022.1067647
- Miao, C., Guo, Q., Fang, X., Chen, Y., Zhao, Y., and Zhang, Q. (2021). Effects of probiotic and synbiotic supplementation on insulin resistance in women with polycystic ovary syndrome: A meta-analysis. *J. Int. Med. Res.* 49, 3000605211031758. doi: 10.1177/03000605211031758
- Moser, B., Milligan, M. A., and Dao, M. C. (2022). The microbiota-Gut-Brain axis: Clinical applications in obesity and type 2 diabetes. *Rev. Invest. Clin.* 74, 302–313. doi: 10.24875/RIC.22000197
- Nasri, F., Doroudchi, M., Jahromi, B. N., and Gharehni-Fard, B. (2018). T Helper cells profile and CD4(+)CD25(+)Foxp3(+)Regulatory T cells in polycystic ovary syndrome. *Iran J. Immunol.* 15, 175–185. doi: 10.22034/IJI.2018.39387
- Page, M. J., Kell, D. B., and Pretorius, E. (2022). The role of lipopolysaccharide-induced cell signalling in chronic inflammation. *Chronic. Stress (Thousand Oaks)*. 6, 24705470221076390. doi: 10.1177/24705470221076390
- Petrillo, T., Semprini, E., Tomatis, V., Arnesano, M., Ambrosetti, F., Battipaglia, C., et al. (2022). Putative complementary compounds to counteract insulin-resistance in PCOS patients. *Biomedicines* 10, 1924. doi: 10.3390/biomedicines10081924

- Qi, X., Yun, C., Liao, B., Qiao, J., and Pang, Y. (2020). The therapeutic effect of interleukin-22 in high androgen-induced polycystic ovary syndrome. *J. Endocrinol.* 245, 281–289. doi: 10.1530/JOE-19-0589
- Qi, X., Yun, C., Pang, Y., and Qiao, J. (2021). The impact of the gut microbiota on the reproductive and metabolic endocrine system. *Gut. Microbes* 13, 1–21. doi: 10.1080/19490976.2021.1894070
- Qi, X., Yun, C., Sun, L., Xia, J., Wu, Q., Wang, Y., et al. (2019). Gut microbiota-bile acid-interleukin-22 axis orchestrates polycystic ovary syndrome. *Nat. Med.* 25, 1225–1233. doi: 10.1038/s41591-019-0509-0
- Qi, X. Y., Yun, C. Y., Sun, L. L., Xia, J. L., Wu, Q., Wang, Y., et al. (2019). Gut microbiota-bile acid-interleukin-22 axis orchestrates polycystic ovary syndrome (vol 25, pg 1225, 2019). *Nat. Med.* 25, 1459–1459. doi: 10.1038/s41591-019-0562-8
- Quaranta, G., Sanguinetti, M., and Masucci, L. (2019). Fecal microbiota transplantation: A potential tool for treatment of human female reproductive tract diseases. *Front. Immunol.* 10. doi: 10.3389/fimmu.2019.02653
- Ravn, P., Gram, F., Andersen, M. S., and Glinborg, D. (2022). Myoinositol vs. metformin in women with polycystic ovary syndrome: A randomized controlled clinical trial. *Metabolites* 12, 1183. doi: 10.3390/metabo12121183
- Roessler, J., Leistner, D. M., Landmesser, U., and Haghikia, A. (2022). Modulatory role of gut microbiota in cholesterol and glucose metabolism: Potential implications for atherosclerotic cardiovascular disease. *Atherosclerosis* 359, 1–12. doi: 10.1016/j.atherosclerosis.2022.08.018
- Sabapathy, T., Helmerhorst, E., Ellison, G., Bridgeman, S. C., and Mamotte, C. D. (2022). High-fat diet induced alterations in plasma membrane cholesterol content impairs insulin receptor binding and signalling in mouse liver but is ameliorated by atorvastatin. *Bba-Mol. Basis. Dis.* 1868, 166372. doi: 10.1016/j.bbadis.2022.166372
- Shen, H. R., Xu, X., Ye, D., and Li, X. L. (2021). Berberine improves the symptoms of DHEA-induced PCOS rats by regulating gut microbiotas and metabolites. *Gynecol. Obstet. Invest.* 86, 388–397. doi: 10.1159/000518040
- Siddiqui, R., Makhlof, Z., Alharbi, A. M., Alfahemi, H., and Khan, N. A. (2022). The gut microbiome and female health. *Biol. (Basel)*. 11, 1683. doi: 10.3390/biology11111683
- Sirmans, S. M., and Pate, K. A. (2013). Epidemiology, diagnosis, and management of polycystic ovary syndrome. *Clin. Epidemiol.* 6, 1–13. doi: 10.2147/CLEP.S37559
- Sugawara, Y., Kanazawa, A., Aida, M., Yoshida, Y., Yamashiro, Y., and Watada, H. (2022). Association of gut microbiota and inflammatory markers in obese patients with type 2 diabetes mellitus: Post hoc analysis of a symbiotic interventional study. *Biosci. Microbiota. Food Health* 41, 103–111. doi: 10.12938/bmfh.2021-081
- Szukiewicz, D., Trojanowski, S., Kociszewska, A., and Szewczyk, G. (2022). Modulation of the inflammatory response in polycystic ovary syndrome (PCOS)-searching for epigenetic factors. *Int. J. Mol. Sci.* 23, 14663. doi: 10.3390/ijms232314663
- Tan, C., Yan, Q., Ma, Y., Fang, J., and Yang, Y. (2022). Recognizing the role of the vagus nerve in depression from microbiota-gut brain axis. *Front. Neurol.* 13, 1015175. doi: 10.3389/fneur.2022.1015175
- Tedesco, S., Adorni, M. P., Ronda, N., Cappellari, R., Mioni, R., Barbot, M., et al. (2019). Activation profiles of monocyte-macrophages and HDL function in healthy women in relation to menstrual cycle and in polycystic ovary syndrome patients. *Endocrine* 66, 360–369. doi: 10.1007/s12020-019-01911-2
- Torres, P. J., Ho, B. S., Arroyo, P., Sau, L., Chen, A., Kelley, S. T., et al. (2019). Exposure to a healthy gut microbiome protects against reproductive and metabolic dysregulation in a PCOS mouse model. *Endocrinology* 160, 1193–1204. doi: 10.1210/en.2019-00050
- Vaez, S., Parivv, K., Amidi, F., Rudbari, N. H., Moini, A., and Amini, N. (2022). Quercetin and polycystic ovary syndrome; inflammation, hormonal parameters and pregnancy outcome: A randomized clinical trial. *Am. J. Reprod. Immunol* 89(3):e13644. doi: 10.1111/aji.13644
- Wang, X., Eguchi, A., Yang, Y., Chang, L., Wan, X., Shan, J., et al. (2023). Key role of the gut-microbiota-brain axis via the subdiaphragmatic vagus nerve in demyelination of the cuprizone-treated mouse brain. *Neurobiol. Dis.* 176, 105951. doi: 10.1016/j.nbd.2022.105951
- Witchel, S. F., Azziz, R., and Oberfield, S. E. (2022). History of polycystic ovary syndrome, premature adrenarche, and hyperandrogenism in pediatric endocrinology. *Horm. Res. Paediatr.* 95, 557–567. doi: 10.1159/000526722
- Wu, H., Wang, X., Fang, X., Lian, F., Li, M., Liao, J., et al. (2022). Metformin modulates the gut microbiome in a mice model of high-fat diet-induced glycolipid metabolism disorder. *BMJ Open Diabetes Res. Care* 10, e003149. doi: 10.1136/bmjdr-2022-003149
- Xu, M. Y., Guo, C. C., Li, M. Y., Lou, Y. H., Chen, Z. R., Liu, B. W., et al. (2022). Brain-gut-liver axis: Chronic psychological stress promotes liver injury and fibrosis via gut in rats. *Front. Cell Infect. Microbiol.* 12, 1040749. doi: 10.3389/fcimb.2022.1040749
- Xue, J., Li, X., Liu, P., Li, K., Sha, L., Yang, X., et al. (2019). Inulin and metformin ameliorate polycystic ovary syndrome via anti-inflammation and modulating gut microbiota in mice. *Endocr. J.* 66, 859–870. doi: 10.1507/endocrj.EJ18-0567
- Yang, Y. Q., Xia, J., Yang, Z., Wu, G. X., and Yang, J. (2021). The abnormal level of HSP70 is related to Treg/Th17 imbalance in PCOS patients. *J. Ovarian Res.* 14, 155. doi: 10.1186/s13048-021-00867-0
- Yde, C. C., Jensen, H. M., Christensen, N., Servant, F., Lelouvier, B., Lahtinen, S., et al. (2021). Polydextrose with and without bifidobacterium animalis ssp. lactis 420 drives the prevalence of akkermansia and improves liver health in a multi-compartmental obesogenic mice study. *PLoS One* 16, e0260765. doi: 10.1371/journal.pone.0260765
- Yin, Y., Guo, Q., Zhou, X., Duan, Y., Yang, Y., Gong, S., et al. (2022). Role of brain-gut-muscle axis in human health and energy homeostasis. *Front. Nutr.* 9, 947033. doi: 10.3389/fnut.2022.947033
- Yu, Z., Qin, E., Cheng, S., Yang, H., Liu, R., Xu, T., et al. (2022). Gut microbiome in PCOS associates to serum metabolomics: a cross-sectional study. *Sci. Rep.* 12, 22184. doi: 10.1038/s41598-022-25041-4
- Zeng, B., Lai, Z., Sun, L., Zhang, Z., Yang, J., Li, Z., et al. (2019). Structural and functional profiles of the gut microbial community in polycystic ovary syndrome with insulin resistance (IR-PCOS): a pilot study. *Res. Microbiol.* 170, 43–52. doi: 10.1016/j.resmic.2018.09.002
- Zhang, F. F., Mao, T., Cui, P., Tamadon, A., He, S., Huo, C. B., et al. (2019). Diversity of the gut microbiota in dihydrotestosterone-induced PCOS rats and the pharmacologic effects of Diane-35, probiotics, and berberine. *Front. Microbiol.* 10. doi: 10.3389/fmicb.2019.00175
- Zhang, M. M., Hu, R. A., Huang, Y. J., Zhou, F. R., Li, F., Liu, Z., et al. (2022). Present and future: Crosstalks between polycystic ovary syndrome and gut metabolites relating to gut microbiota. *Front. Endocrinol.* 13. doi: 10.3389/fendo.2022.933110
- Zhang, Q., and Hu, N. (2020). Effects of metformin on the gut microbiota in obesity and type 2 diabetes mellitus. *Diabetes Metab. Syndr. Ob.* 13, 5003–5014. doi: 10.2147/DMSO.S286430
- Zhang, S., Tu, H., Yao, J., Le, J., Jiang, Z., Tang, Q., et al. (2020). Combined use of Diane-35 and metformin improves the ovulation in the PCOS rat model possibly via regulating glycolysis pathway. *Reprod. Biol. Endocrinol.* 18, 58. doi: 10.1186/s12958-020-00613-z
- Zhao, C., Hu, X., Bao, L., Wu, K., Feng, L., Qiu, M., et al. (2021). Aryl hydrocarbon receptor activation by lactobacillus reuteri tryptophan metabolism alleviates escherichia coli-induced mastitis in mice. *PLoS Pathog.* 17, e1009774. doi: 10.1371/journal.ppat.1009774
- Zhao, C. J., Bao, L. J., Qiu, M., Wu, K. Y., Zhao, Y. H., Feng, L. J., et al. (2022). Commensal cow roseburia reduces gut-dysbiosis-induced mastitis through inhibiting bacterial translocation by producing butyrate in mice. *Cell Rep.* 41, 111681. doi: 10.1016/j.celrep.2022.111681
- Zhao, H. Y., Chen, R. F., Zheng, D. X., Xiong, F., Jia, F., Liu, J. Y., et al. (2022). Modified banxia xixin decoction ameliorates polycystic ovarian syndrome with insulin resistance by regulating intestinal microbiota. *Front. Cell Infect. Mi.* 12, 854796. doi: 10.3389/fcimb.2022.854796
- Zhao, M. K., Jiang, G., Zhou, H., Li, J. Q., Xiang, W., Li, S. J., et al. (2022). Gut microbiota: a potential target for improved cancer therapy. *J. Cancer Res. Clin* 149(1):541–552. doi: 10.1007/s00432-022-04546-5
- Zhao, X. X., Jiang, Y. P., Xi, H. Y., Chen, L., and Feng, X. L. (2020). Exploration of the relationship between gut microbiota and polycystic ovary syndrome (PCOS): a review. *Gebursh. Frauenheilk.* 80, 161–171. doi: 10.1055/a-1081-2036
- Zhou, L., Ni, Z., Cheng, W., Yu, J., Sun, S., Zhai, D., et al. (2020). Characteristic gut microbiota and predicted metabolic functions in women with PCOS. *Endocr. Connect.* 9, 63–73. doi: 10.1530/EC-19-0522
- Zhu, Y., Li, Y., Liu, M., Hu, X. D., Zhu, H. Q., and Wan, G. F. (2020). Chinese Herbal medicine, ameliorates insulin sensitivity in PCOS model rats with insulin resistance via remodeling intestinal homeostasis. *Front. Endocrinol.* 11. doi: 10.3389/fendo.2020.00575
- Zuo, K., Fang, C., Liu, Z., Fu, Y., Liu, Y., Liu, L. F., et al. (2022). Commensal microbe-derived SCFA alleviates atrial fibrillation via GPR43/NLRP3 signaling. *Int. J. Biol. Sci.* 18, 4219–4232. doi: 10.7150/ijbs.70644