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CLINICAL RESEARCH

Meta-Analysis of the Endocrine and Metabolic Effects of Probiotics on Polycystic Ovary Syndrome

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ABSTRACT

OBJECTIVE

Systematic evaluation of the application of probiotics in the treatment of polycystic ovary syndrome (PCOS).

METHODS

Computer searches of PubMed, The Cochrane Library, Web of Science, Medline, Embase, Ovid, CNKI, Wan Fang Data, and VIP databases were conducted to retrieve RCT studies on probiotics for the treatment of patients with PCOS from the time of database creation to March 2021. Meta-analysis was performed by two researchers after screening, extracting, and evaluating the literature using revman 5.3 software.

RESULTS

A total of 13 studies were included, and the results of Meta-analysis showed that compared with the placebo group, probiotic supplementation increased sex hormone binding globulin (SHBG) and insulin sensitivity testing index (QUICKI) and decreased fasting insulin (INS), total testosterone (TT), insulin resistance index (HOMA-IR), fasting blood glucose (FPG), low-density lipoprotein (LDL-C), triglyceride (TG), and total cholesterol (TC) levels in PCOS patients ($P<0.05$); there was no significant effect on deoxyepiandrosterone sulfate (DHEAS), high-density lipoprotein (HDL-C), and hyper-sensitive c-reactive protein (HS-CRP) levels in PCOS patients ($P>0.05$).

CONCLUSION

Probiotics may improve serum levels of endocrine and metabolism-related indicators in patients with PCOS, but further investigation and validation in large samples and high-quality RCT studies are needed.

KEYWORD

Polycystic ovary syndrome; Probiotics; Prebiotics; Meta-analysis

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, with a prevalence of 6%-10%, according to the Rotterdam criteria, the incidence of PCOS has reached 15% [1,2]. Typical patients with polycystic ovary syndrome present with a range of metabolic abnormalities characterized by insulin resistance, lipid abnormalities, and increased inflammation [2,3], and elevated insulin resistance and inflammatory markers (e.g., c-reactive protein CRP) in women with PCOS are strongly associated with the development of metabolic syndrome, type 2 diabetes, and cardiovascular disease [4-6]. Therefore, it is particularly important to improve endocrinology and metabolism in patients with PCOS.

In recent years, research on the etiology and treatment of PCOS has been constantly updated and developed at home and abroad. It has been shown that probiotic supplementation has an impact on the treatment of patients with PCOS, and that supplementation improves metabolic syndrome, insulin resistance and CRP in patients [7,8], but the effect of probiotics on glycemic control and CRP levels in women with polycystic ovary syndrome is controversial [9,10]. Therefore, this study will systematically review the relevant domestic and international literature to evaluate the effects of probiotic supplementation on blood glucose, lipids, inflammation, and hormone levels in patients with PCOS, and provide a scientific basis for future clinical treatment [11-23].

MATERIALS AND METHOD

Search Strategy

Computer searches of PubMed, The Cochrane Library, Web of Science, Medline, Embase, Ovid, CNKI, Wan Fang Data, VIP databases for "Polycystic Ovary Syndrome ", "PCOS", "polycystic ovarian syndrome", "Probiotics ", "Prebiotic", "synbiotic", "symbiotic the search of domestic and foreign databases was based on a combination of subject terms and free words such as "supplementation", "polycystic ovarian syndrome" and "probiotic". In addition, the references of the included literature were manually searched to obtain relevant literature.

Inclusion and Exclusion Criteria of the Literature

Inclusion criteria

(1) The type of literature was a randomized controlled trial (RCT); (2) The study population was PCOS patients who met the Rotterdam criteria [11] or the National Institutes of Health (NIH) criteria [12]. (3) The intervention was supplementation with probiotics, prebiotics or synthetics for the experimental group and placebo treatment for the control group.

Exclusion criteria

(1) Duplicate publications; (2) Literature for which complete experimental data were not available; (3) Animal experiments, reviews, and other literature.

Literature Extraction

The literature search, extraction and quality evaluation were performed by 2 researchers separately, and in case of disagreement, the decision was made after discussion or with the participation of a third researcher. Data extraction included: (1) Basic information: Author, year of publication, country, etc., (2) Age, BMI, number of cases, probiotic supplementation dose and duration of study subjects, (3) Outcome indicators: Endocrine

indicators [fasting insulin (INS), insulin resistance index (HOMA-IR), insulin sensitivity testing index (QUICKI), total testosterone (TT), deoxyepiandrosterone sulfate (DHEAS), sex hormone binding globulin (SHBG); metabolic indexes [fasting blood glucose (FPG), ultrasensitive c-reactive protein (hs-CRP), total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C).

Quality Evaluation

Independent evaluation by 2 investigators based on the Cochrane Collaboration Network's assessment tool and cross-checking of results, including randomization methods, allocation concealment, blinding, completeness of results, selective reporting, and other risks of bias.

Statistical Analysis

Mate analysis was performed using RevMan 5.3 software, and quantitative information was expressed as weighted mean difference (WMD) or standardized mean difference (SMD), and categorical information was expressed as dominance ratio (OR) or relative risk ratio (RR). Interval estimation was performed at 95% CI, and differences were considered statistically significant at P<O.05. Heterogeneity tests were determined using I2 and P values; if I2 <50% or P >0.05, this indicated less heterogeneity and a fixed-effects model was used, and conversely, a random-effects model was used. If there was significant clinical heterogeneity, subgroup analysis and sensitivity analysis were required. Estimation of the presence of publication bias using funnel plots.

RESULTS

Literature Search Results

Initially, 588 articles were retrieved, and a total of 13 RCT articles were screened for inclusion in the study, including a total of 862 patients, and all 13 articles were in English. The literature screening process and results are shown in Figure 1.

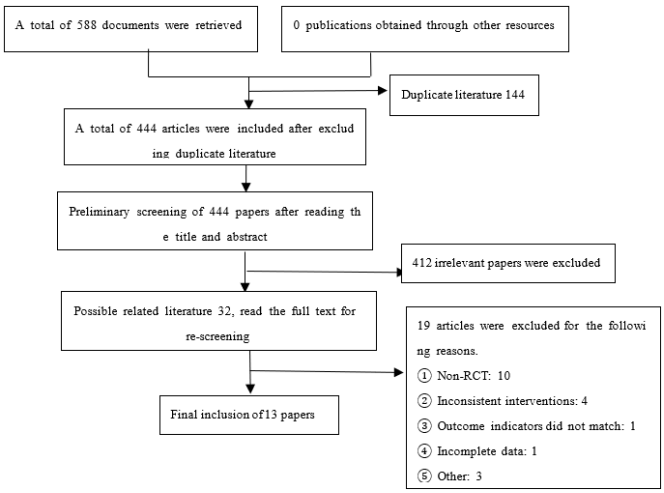

Figure 1: Flow chart of literature screening.

Basic Characteristics of the Included Literature and the Results of the Risk of Bias Evaluation

The basic characteristics of the included literature are shown in Table 1, and the results of the risk of bias evaluation are shown in Figure 2.

Table 1: General information of the included literature.

Number of		BMI	Intervention time (T/C; kg/m^2)	Interventions
Cases (T/C)	Age (T/C)			T/C
30/30	25.2±5.4/24.8±5.1	25.3±4.2/12 weeks	26.4±4.3	Probiotic capsules containing *Lactobacillus acidophilus*, *Placebo Lactobacillus casei*, *Bifidobacterium bifidum* (2×10^9 CFU/g).
30/30	30.06±1.06/28.96±0.98	26.84±0.53/12 weeks	25.97±0.42	Probiotic capsule (100mg) containing *Lactobacillus acidophilus*, *Placebo Lactobacillus plantarum fermentum*, *Lactobacillus griseus* (1×10^9 CFU/g).
30/30	26.0±5.3/25.6±3.8	24.6±3.3/12 weeks	24.0±3.0	Probiotic capsules contain *Lactobacillus acidophilus*, *Placebo Lactobacillus royi*, *Lactobacillus fermentum*, *Bifidobacterium bifidum* (2×10^9 CFU/g) + 200 mcg selenium.
30/30	27.2±4.6/27.7±4.7	23.7±3.6/12 weeks	23.6±3.5	Probiotic capsules containing *Lactobacillus acidophilus*, *Lactobacillus Placebo casei*, *Bifidobacterium bifidum* (2×10^9 CFU/g).
50/49	28.1±5.5/29.0±5.1	32.89±6.11/12 weeks	32.0±4.23	Probiotic capsule (500 mg) containing *Lactobacillus acidophilus* (3×10^9 CFU/g); *Lactobacillus casei* (3×10^9CFU/g), *Placebo Lactobacillus bulgaricus* (5×10^8 CFU/g) *Lactobacillus rhamnosus* (7×10^9 CFU/g), *Bifidobacterium longum* (7×10^9 CFU/g).
30/30	25.7±5.5/25.9±5.2	27.4±4.0/12weeks	27.2±5.3	*Bifidobacterium shortum* (2×10^9 CFU/g), *Streptococcus thermophilus* (3×10^8 CFU/g) + Probiotic inulin Combination capsules contain *Lactobacillus acidophilus*, *Placebo Lactobacillus casei, and Bifidobacterium bifidum* (2×10^9 CFU/g) + 800 mg inulin.
30/30	27.0±5.6/27.3±6.1	27.3±3.8/12 weeks	27.5±5.3	The capsules contain *Lactobacillus acidophilus*, *Placebo Lactobacillus casei Bifidobacterium bifidum* (2×10^9 CFU/g) + 800 mg inulin.
30/30	27.7±6.9/26.8±5.1	24.8±5.0/12 weeks	25.5±3.9	Probiotic capsules contain *Lactobacillus acidophilus*, *Placebo Lactobacillus royale*, *Lactobacillus fermentum*, *Bifidobacterium bifidum* (2×10^9 CFU/g) + 200 mcg selenium.
32/33	26.5±0.1/25.72±0.1	26.06±0.1/8 weeks	25.8±0.1	Probiotic capsule (500mg) contains *Lactobacillus casei* (7×10^9 CFU/g) *Placebo Lactobacillus acidophilus* (2×10^9 CFU/g), *Lactobacillus rhamnosus* (1.5×10^9 CFU/g), *Lactobacillus bulgaricus* (2×10^8 CFU/g) *Bifidobacterium shortum* (2×10^{10} CFU/g), *Bifidobacterium longum* (7×10^9 CFU/g) *Streptococcus thermophilus* (1.5×10^9 CFU/g).
30/30	24.4±4.7/25.4±5.1	24.3±4.2/12 weeks	25.1±4.9	Probiotic capsule contains *Lactobacillus acidophilus*, *Placebo Lactobacillus royi*, *Lactobacillus fermentum Bifidobacterium bifidum* (2×10^9 CFU/g) + 50,000 units of vitamin D.
31/31	28±6.3/26±6.2	25±4.4/3 Months	27±5.6	The prebiotic group ingested 20 grams of resistant dextrin dissolved Placebo in a glass of water per day, and Placebo group ingested 20 grams of maltose dextrin dissolved in one cup of water per day.
34/34	30.4±5.82/28.6±4.8	29.43±5.69/8 weeks	28.47±3.55	Combination capsule (500 mg) contains *Lactobacillus Placebo casei* (3×10^9 CFU/g), *Lactobacillus rhamnosus* (7×10^9 CFU/g), *Lactobacillus bulgaricus* (5×10^8 CFU/g), *Lactobacillus acidophilus* (3×10^{10} CFU/g), *Bifidobacterium longum* (1×10^9 CFU/g), strain ACS-071-V-Sch8b (2×1010 CFU/g), *Streptococcus thermophilus* (3×108 CFU/g) and inulin-type prebiotics.
44/44	28.1±5.5/29±5.1	32.89±6.11/12 weeks	32±4.23	*Lactobacillus acidophilus* (3×10^{10} CFU/g), *Lactobacillus casei Placebo* (3×10^9 CFU/g), *Lactobacillus bulgaricus* (5×10^8 CFU/g), *Lactobacillus rhamnosus* (500 mg) (3×10^9 CFU/g), *Lactobacillus bulgaricus* (5×10^8 CFU/g), *Lactobacillus rhamnosus* (7×10^9 CFU/g), *Bifidobacterium longum* (1×10^9 CFU/g), *Bifidobacterium shortum* (2×10^{10} CFU/g), *Streptococcus thermophilus* (3×10^8 CFU/g) and prebiotic inulin.

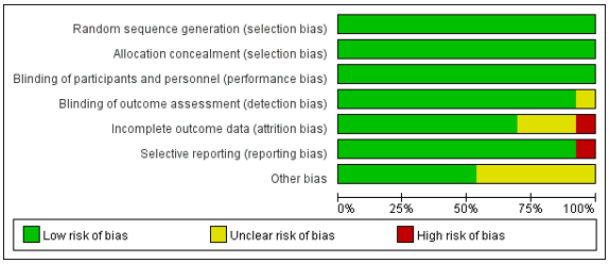

Figure 2: Risk of bias evaluation results of the included literature.

Meta-Analysis Results

Effect of probiotic supplementation on endocrine indexes in PCOS patients The combined results showed that probiotic supplementation increased SHBG and QUICKI and decreased INS, TT, and HOMA-IR levels in PCOS patients compared with placebo (P <0.05); there was no significant effect on DHEAS levels in PCOS patients (P >0.05), as shown in Table 2.

Table 2: Meta-analysis of endocrine index results of PCOS patients in the probiotic and placebo groups.

Indicators	Probiotic group, n	Placebo group, n	RMS estimation	P	Heterogeneity test	
			SMD（95%CI）		P	I^2
QUICKI	172	172	2.10(0.72～3.48)	0.003	0.00001	97%
HOMA-IR	206	206	-0.57(-0.98～-0.15)	0.007	0.0008	76%
INS	206	206	-0.52(-0.93～-0.12)	0.01	0.001	76%
TT	120	120	-0.24(-0.35～-0.13)	0.0001	0.001	81%
DHEAS	91	91	0.02(-0.36～0.39)	0.93	0.19	39%
SHBG	120	120	0.51(0.03～0.99)	0.94	0.02	70%

Effect of Probiotic Supplementation on Metabolic Indexes in PCOS Patients

The combined results showed that probiotic supplementation reduced the levels of FPG, LDL-C, TG, and TC compared with placebo (P <0.05); there was no significant effect on the levels of HDL-C and HS-CRP in PCOS patients (P >0.05), as shown in Table 3.

Table 3: Meta-analysis of metabolic index results of PCOS patients in the probiotic and placebo groups.

Indicators	Probiotic group, n	Placebo group, n	RMS estimation	P	Heterogeneity test	
			SMD（95%CI）		P	I^2
TC	199	199	-1.25(-2.22～-0.28)	0.01	0.00001	95%
LDL-C	199	199	1.12(0.04～-2.20)	0.04	0.00001	96%
HDL-C	199	199	0.48(-0.47～1.43)	0.32	0.00001	95%
TG	199	199	-0.86(-1.69～-0.02)	0.04	0.00001	93%
FPG	203	203	-1.65(-2.80～-0.49)	0.05	0.00001	96%
HS-CRP	213	214	-0.68(-1.61～0.26)	0.16	0.00001	95%

Subgroup Analysis

Subgroup analyses were performed on the type of intervention (probiotic and co-biotic groups) and duration of intervention (≥12 weeks and <12 weeks) of the included studies according to the heterogeneity present in the included literature, as shown in Table 4.

Table 4: Subgroup analysis of probiotic group versus placebo group for outcome indicators in PCOS patients.

Indicators	Number of included Literature	Subgroup	95%CI (%)	I^2	Overall I^2 (%)
QUICKI	Type of Intervention 4 1 Intervention time 4 1	Probiotic group Hapten group ≥12weeks ＜12weeks	0.68～4.20 0.69～1.80 0.03～1.04 8.76～12.68	97 - 77 -	97

HOMA-IR	Type of Intervention 4 2 Intervention time 4 2	Probiotic group Hapten group ≥12weeks ＜12weeks	-1.17～0.06 -1.03～-0.18 -0.75～-0.01 -1.99～0.13	84 30 58 88	76
INS	Type of Intervention 4 2 Intervention time 4 2	Probiotic group Hapten group ≥12weeks ＜12weeks	-1.11～0.09 -1.04～-0.08 -0.78～0.04 -1.81～0.16	84 44 65 87	76
TT	Type of Intervention 3 1 Intervention time 4 -	Probiotic group Hapten group ≥12weeks ＜12weeks	-0.37～-0.15 -0.38～0.58 -0.35～-0.13 -	86 - 81 -	81
SHBG	Type of Intervention 3 1 Intervention time 4 -	Probiotic group Hapten group ≥12weeks ＜12weeks	-0.15～0.86 0.46～1.54 0.03～0.99 -	65 - - -	70
TC	Type of Intervention 3 3 Intervention time 5 1	Probiotic group Hapten group ≥12weeks ＜12weeks	-5.23～-0.19 -0.42～0.11 - -2.76～-0.35	98 0 96 -	95
LDL-C	Type of Intervention 3 3 Intervention time 5 1	Probiotic group Hapten group ≥12weeks ＜12weeks	-0.51～0.44 0.55～6.76 -0.38～0.16 0.19～2.93	- 98 0 96	96
TG	Type of Intervention 3 3 Intervention time 5 1	Probiotic group Hapten group ≥12weeks ＜12weeks	-0.54～0.41 -3.64～0.19 -0.34～0.19 -2.06～0.02	- 97 0 95	93
FPG	Type of Intervention 5 1 Intervention time 5 1	Probiotic group Hapten group ≥12weeks ＜12weeks	-0.62～0.33 -3.35～-0.45 -1.14～-0.10 -3.58～0.04 -3.10～-1.79	(-) 97 - 97 -	96

Sensitivity Analysis

Meta-analysis results showed that the TT indicator after excluding Karamali 2018 literature was (SMD: -0.18; 95% CI: -0.30 to -0.07), the HOMA-IR indicator after excluding Shoaei 2015 literature was (SMD: -0.38; 95% CI: -0.67 to -0.09), the SHBG indicator after excluding SHBG index after exclusion of Ostadmohammadi 2019 literature was (SMD: 0.72; 95% CI: 0.41 to 1.04), and TC index after exclusion of Ostadmohammadi 2019 literature was (SMD: -0.30; 95% CI: -0.52 to -0.07) (Table 5).

Table 5: Sensitivity analysis of the probiotic group versus the placebo group for outcome indicators in PCOS patients.

Indicators	**Before sensitivity analysis**			**After sensitivity analysis**		
	Inclusion in the literature	**SMD**	**95%CI**	**SMD**	**95%CI**	**Exclusion of literature**
QUICKI	5	2.1	0.72～3.48	0.54	0.03～1.04	Shoaei 2015
HOMA-IR	6	-0.57	-0.98～-0.15	-0.38	-0.67～-0.09	Shoaei 2015
INS	6	-0.52	-0.93～-0.12	-0.35	-0.67～-0.04	Shoaei 2015
TT	4	-0.24	-0.35～-0.13	-0.18	-0.30～-0.07	Karamali 2018
SHBG	4	0.51	0.03～0.99	0.72	0.41～1.04	Ostadmohammadi 2019
TC	6	-1.25	-2.22～-0.28	-0.3	-0.52～-0.07	Ostadmohammadi 2019
LDL-C	6	1.12	0.04～-2.20	-0.15	-0.36～0.07	Ostadmohammadi 2019
TG	6	0.86	-1.69～-0.02	-0.22	-0.46～0.02	Ostadmohammadi 2019

Publication Bias Test

Due to the small number of studies included for individual outcome indicators, no publication bias test was performed in this study.

DISCUSSION

Polycystic ovary syndrome (PCOS) is an endocrine metabolic syndrome with complex etiology and diverse clinical manifestations and is one of the most common causes of endocrine disorders and infertility in women of reproductive age. The etiology of PCOS is unknown and may be related to genetics, lifestyle and other factors [25]. Studies have shown that intestinal flora is closely related to the level of endocrine metabolism in humans, and dysbiosis of intestinal flora can increase androgen levels, lead to insulin resistance, cause chronic inflammation, obesity, and other metabolic syndromes. Therefore, regulation of intestinal flora and supplementation of probiotics have certain adjuvant and therapeutic effects on PCOS disease [26-29]. In recent years, probiotics have received wide attention in regulating the balance of intestinal flora, controlling and managing blood glucose and lipid levels, and regulating inflammation and hormones. Foreign studies on RCTs of probiotics in PCOS patients have been increasing, but studies related to the effects of probiotics in PCOS patients are not the same. Therefore, this study will systematically evaluate the effects of probiotics on glucose, lipid, inflammation and hormone levels in patients with PCOS, and thus provide a relevant scientific basis for clinical treatment.

Effect of Probiotics on Endocrine Indexes in PCOS Patients

The results of this study showed that probiotic supplementation increased SHBG and QUICKI and decreased INS, TT, and HOMA-IR levels in PCOS patients, but had no significant effect on DHEAS levels in PCOS patients. Pathophysiological mechanisms suggest that PCOS patients are prone to glucose intolerance and impaired insulin sensitivity, and the intake of probiotics or synbiotics balances the intestinal microbial community and intestinal pH, improves the intestinal catabolism and metabolism of starch, and enhances intestinal digestion and absorption of nutrients [30], thus lowering blood glucose and reducing insulin resistance, however, the exact glucose-lowering effect of probiotics mechanism of the hypoglycemic effect of probiotics is still not fully understood [31]. Some studies have shown that probiotic supplementation significantly reduces blood glucose, insulin and insulin resistance levels in diabetic patients [32-34]. However, a meta-analysis by Javad Heshmati showed no effect of probiotic supplementation on insulin resistance levels in patients with PCOS [35]. This may be due to the different pathophysiological mechanisms in diabetic patients and PCOS patients; therefore, more studies are needed to demonstrate the effect of probiotics on insulin levels in PCOS. Cholesterol, a prerequisite for androgen production in PCOS patients, leads to increased androgen levels [22,36], and probiotics lower cholesterol by reducing cholesterol production in the liver, which in turn reduces androgen production, such as testosterone, DHEAS, and SHBG levels [22,37,38]. Shamasbi SG et al. showed that intake of probiotics or co-biotics in PCOS patients had significantly lower serum testosterone, SHBG, and DHEAS [39]. However, the present study showed no effect of probiotics on DHEAS, which may be related to the short duration of intervention in the included articles or the

small number of included literature; therefore, subsequent RCT clinical trials may further confirm the effect of probiotics on androgen levels by extending the duration of intervention.

Effect of Probiotics on Metabolic Indexes of PCOS Patients

The results of this study showed that probiotic supplementation reduced FPG, LDL-C, TG, and TC levels and had no significant effect on HDL-C and HS-CRP levels in patients with PCOS. CRP is an important inflammatory factor in diabetes and other metabolic diseases [40], and probiotics can exert anti-inflammatory and antioxidant effects by producing short-chain fatty acids in the gut [41], and prebiotics (e.g., Oligofructose) act by reducing oxidative and inflammatory markers in the liver [42]. Some studies have demonstrated that probiotic supplementation reduces inflammatory factors and CRP levels [43], but the Meta-analysis by Reza Tabrizi et al. found that probiotic supplementation given with PCOS did not affect CRP levels [44], which is consistent with the results of the present study. Therefore, more RCT studies are still needed to confirm whether probiotics can reduce the inflammatory response in PCOS. The beneficial effect of probiotics or synbiotics on lipids may be due to blocked cholesterol absorption [45] and the inhibition of bile acid reabsorption in the lumen [46,47], and the mechanism by which probiotics lower TG and elevate HDL-C levels is not clear. Previous studies have confirmed that probiotics can significantly reduce TC, TG and LDL-C values [48], and a meta-analysis showed no effect of probiotic supplementation on HDL-C [49], which is consistent with the results of the present study, but the results of Li et al. [50] showed that probiotics can elevate HDL-C; therefore, this conclusion needs further validation.

Limitations of this Study

1. Most of the included studies were from Iran, and the generalizability of the results may be affected by factors such as ethnic differences and lifestyle, therefore, it is recommended that more countries conduct RCTs to confirm the results.
2. The number of included literature is insufficient and the sample size is small, which may produce some heterogeneity in the results.
3. The interventions in the included studies were slightly different, such as the dose and type of probiotic supplementation and the duration of intervention, and also the units of measurement for each outcome varied, which may be an important source of heterogeneity.
4. The outcome metrics of the included studies varied, and the small number of included literature for certain outcome metrics (e.g., DHEAS) may have influenced the results.

In conclusion, the preliminary evidence from this Meta-analysis suggests that probiotic supplementation can improve the levels of endocrine and metabolism-related indicators in PCOS patients, but due to various limitations of this study, more large-sample, high-quality randomized controlled trials are needed in the future to evaluate the efficacy of probiotic supplementation in PCOS patients.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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