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Review Article

The Role of Probiotics, Prebiotics and Synbiotics on Polycystic Ovary Syndrome

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Abstract

Polycystic ovary syndrome is a heterogeneous and multifactorial endocrine condition among women of childbearing age impeding infertility. The global prevalence of PCOS varies between 6-26%. Typical symptoms include hyperandrogenism, hyperinsulinemia, hirsutism, and ovarian dysfunction. This article reviews the effects of probiotics, prebiotics, and synbiotics supplementation on females suffering from PCOS keeping in view the most recent findings. Data was collected from 7 databases from the literature published until June 2023. The MeSH nomenclature was used in the search approach. After reviewing all the collected studies, 7 studies were selected for the review. Recent studies have proposed the association of PCOS pathogenesis with dysbiosis of gut microbiota. The use of pro, pre, and synbiotics has shown improvement in the symptoms by restoring the balance of gut microbiota. Among the many available probiotics, lactic acid-producing bacteria, e.g. *L. plantarum HL2 and CCFM1019, B. lactis,* and *B. longum HB3* have been reported to be the most useful probiotics.

Key words: Polycystic ovary syndrome, probiotics, prebiotics, synbiotics.

Introduction

Polycystic ovarian syndrome (PCOS) is one of the most prevalent gynecologic and endocrine conditions among women of childbearing age, commonly regarded as a key contributor to infertility.[1] Globally, it affects 6-26% of women of reproductive age.[2] Excessive body hair, an irregular menstrual cycle or amenorrhea, and infertility are typical symptoms. Additionally, metabolic symptoms such as inflammation, dyslipidemia, β-cell dysfunction, obesity, hyperandrogenism, insulin resistance (IR), glucose intolerance, and inflammation are associated with PCOS. Furthermore, PCOS women likely have a higher risk of heart and brain problems, venous thromboembolism, and ovarian cancer.[3]

Even though environmental, metabolic, neuroendocrine, and genetic factors have all been suggested as contributors to PCOS occurrence, the exact pathophysiology of PCOS is still unknown. Recent research, however, suggests the possibility that PCOS, obesity, metabolic syndrome, and diabetes mellitus may be related to the changes in gut microflora composition. A greater understanding of how the intestinal microbiota is linked with the pathogenesis of PCOS, researchers have recently focused on the use of microbiota-targeted drugs like probiotics, prebiotics, and synbiotics to control PCOS.[1]

Living microorganisms known as probiotics are beneficial for health if taken enough and help maintain the gut microorganisms in balance. Major probiotics useful in the control of PCOS are lactic-acid-producing bacteria species, including *Lactobacillus* and *Bifidobacterium*.[4] Prebiotics are indigestible, non-fermentable substances that improve the health of the host by raising beneficial gut bacteria and decreasing the combination and activity of bad bacteria. Inulin, resistant dextrin, oligofructose, galactooligosaccharide, and lactulose are examples of prebiotics.[5] Products containing both probiotics and prebiotics are referred to as synbiotics, such as a product containing

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galactooligosaccharides and *Bifidobacterium*. Synbiotics boost the health of the host by increasing the probiotic's survival rate and introducing beneficial gut microorganisms.[1]

Methodology

Seven databases, including PubMed, Google Scholar, STFM, EMBASE, the Cochrane Library, ProQuest, and the Magiran database, were used for the literature published till June 2023. Related studies from 2017-2023 were collected and the references in the found articles were also used to find further studies. The MeSH nomenclature was used in the search approach. The MeSH terms "PCOS", "Polycystic ovary", "Prebiotics", "Probiotics", "Probiotics influence on PCOS", "Synbiotics", "PCOS diagnosis", "PCOS prevalence", "Causes of PCOS", and "Gut microflora" were used alone or in combination with other keywords.

The studies included in this review were selected based on the criteria; (1) Randomized controlled trials (RCTs), (2) Diagnosis based on NIH or Rotterdam criteria, (3) Participants with a definite diagnosis of PCOS, (4) Intervention of probiotics, prebiotics, or synbiotics separately or in combination with other drugs, (5) Outcome included endocrine and metabolic parameters. A total of 63 relevant records were collected through database searching and an additional 12 records were collected from citations. After removing duplicates, 52 records were screened. After the exclusion of 17 records, 35 full-text articles were assessed for eligibility. Finally, 7 studies were selected for the review (Figure-1).

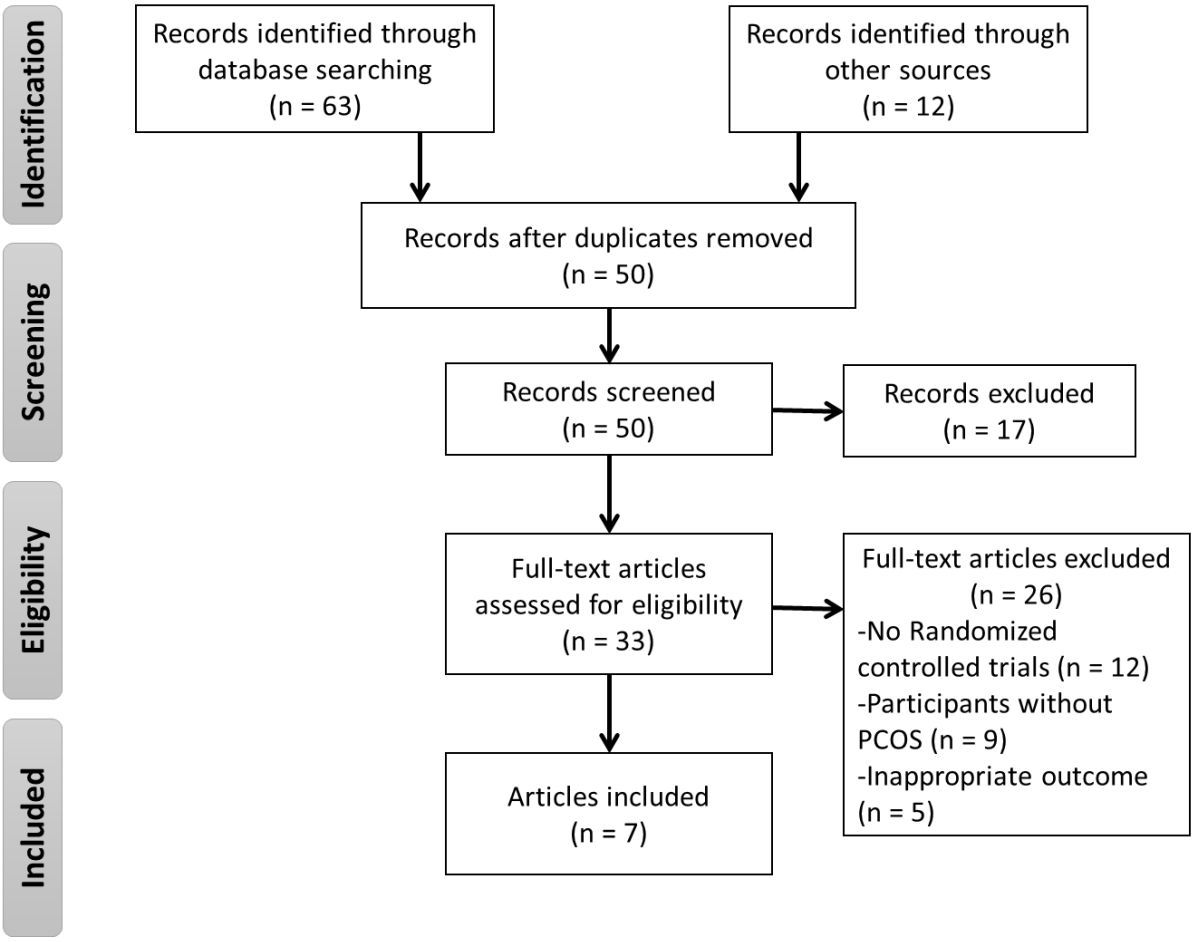

Figure 1: PRISMA flow chart for the study selection process.

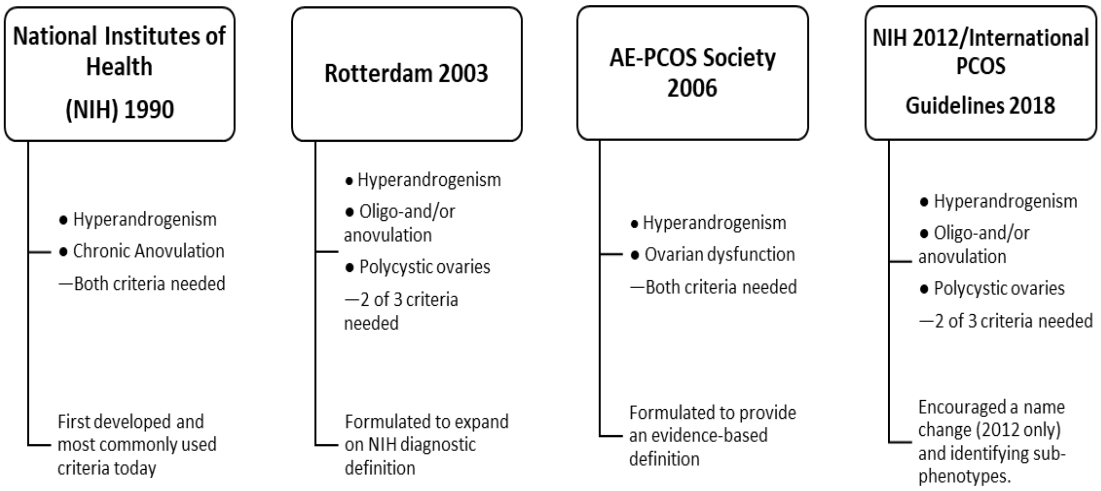

Figure 2: Evolution of diagnostic criteria for polycystic ovarian syndrome.

Diagnostic criteria for PCOS

PCOS can be diagnosed by one of the three available criteria viz, National Institutes of Health (NIH), Rotterdam, and the Androgen Excess - PCOS Society criteria (AE-PCOS Society). The NIH defined the first criteria for PCOS diagnosis in 1990 (Figure-2). It required both chronic anovulation and clinical or biochemical signs of hyperandrogenism to make a diagnosis. In 2003, a revision to the NIH 1990 criteria by a task committee assessing the available evidence in Rotterdam, Netherlands suggested a new set of diagnostic criteria for PCOS that required only two of the three criteria to make a diagnosis including oligo or anovulation, clinical or biochemical hyperandrogenism, and morphological appearance of polycystic ovaries known as the Rotterdam criteria.[6]

In 2009, the AE-PCOS Society put out the most up-to-date diagnostic criteria. A modified version of the criteria proposed: (a) ovarian malfunction (including oligo-anovulation and/or polycystic ovaries), (b) androgen excess (including hirsutism and/or hyperandrogenaemia), and (c) exclusion of additional androgen excess or diseases. The AE-PCOS criteria similarly state that hyperandrogenism-related conditions must be eliminated, but they allow the clinician to consider how frequent they are while conducting testing.[7]

PCOS and the gut microbiota:

The term "microbiota" describes all sorts of microorganisms (bacteria, archaea, protozoa, fungi, etc.) that can be found in various parts of the human body like skin, mouth, respiratory system, gastrointestinal tract, and vagina. The human gut microbiome contains between 10^{13} - 10^{14} different species and 7000 + different types of bacteria. *Bacteroidetes* and *Firmicutes* are the two bacterial species that are most frequently encountered. The delicate balance between the host and the gut microbiota, which profoundly impacts physiology, metabolism, nutrition, and immune function, inhibits the onset of several diseases in physiological settings.[8]

Recent studies on the association between PCOS and alterations in the gut flora have disclosed a huge disparity in the makeup of the gut microbiome that exists among PCOS patients and healthy individuals. Research has revealed that in addition to a change in the microbiome's overall composition, PCOS also involves a change in the balance of particular bacterial species, including Bacteroidetes and Firmicutes.[9] Many studies have found an altered beta diversity and decreased alpha diversity in PCOS patients. Beta (β) diversity tells us the similarity of one community with the other and alpha (α) diversity reflects the no. of species that are present in a community occupying a certain environment and is thought to be an indicator of the health of an ecosystem.[10]

Dysbiosis of gut microbiota and pathways leading to PCOS

Dysbiosis of gut microbiota (DOGMA) is thought to be one of the possible mechanisms of PCOS development. The dysbiosis results in the activation of the immune system which in turn interferes with the proper functioning of the insulin receptors, resulting in hyperinsulinemia. This in turn results in the overproduction of ovarian androgens thereby preventing the normal development of follicles. Two major factors are involved in the

dysbiosis of gut microbiota i.e., obesity and a diet with high fats and low fiber. Obesity among PCOS women is very common having an incidence of 30-70%.[11]

The increased systemic circulation of lipopolysaccharides is known as metabolic endotoxemia and is associated with chronic inflammation and cardiometabolic variations. It is caused by the translocation of the endotoxins from the intestine into circulation due to increased intestinal permeability as a result of increased amounts of proinflammatory cytokines such as tumor necrosis factor-alpha TNF-α and interleukin-6 (IL-6).[12] In obese women, there is an excessive translocation of gram-negative bacteria into the circulation leading to chronic endotoxemia with excessive bacterial LPS in circulation. The nuclear factor kappa B (NF-kB) pathway is activated in response to the recognition of these LPS by Toll-like receptors (TLR) on the surface of the enterocytes which causes inflammation. The translocation of LPS is also reported to be caused by high-fat diets.[13]

Insulin resistance is also considered a possible pathway that is caused by chronic inflammation and is associated with increased intestinal permeability, lipopolysaccharide (LPS) circulation, and TNF-α and IL-6 levels.[14] The serum testosterone levels are elevated as a result of insulin resistance, firstly by increased androgen production by the ovaries and secondly by increasing free testosterone while decreasing the sex hormone binding globulin (SHBG). This in turn results in acne and hirsutism. Moreover, the amounts of free insulin-like growth factor 1 (IGF-1) are also increased by hyperinsulinemia which prevents the production of IGF-1 binding protein and stimulates androgen production by singleton cells. The increased amounts of insulin and IGF-1 result in polycystic ovaries formation, menstrual irregularity, and prevention of normal follicle formation.[8]

Another pathway leading to the pathogenesis of PCOS may be the regulation of the inflammation pathway and gut-brain stimulation by

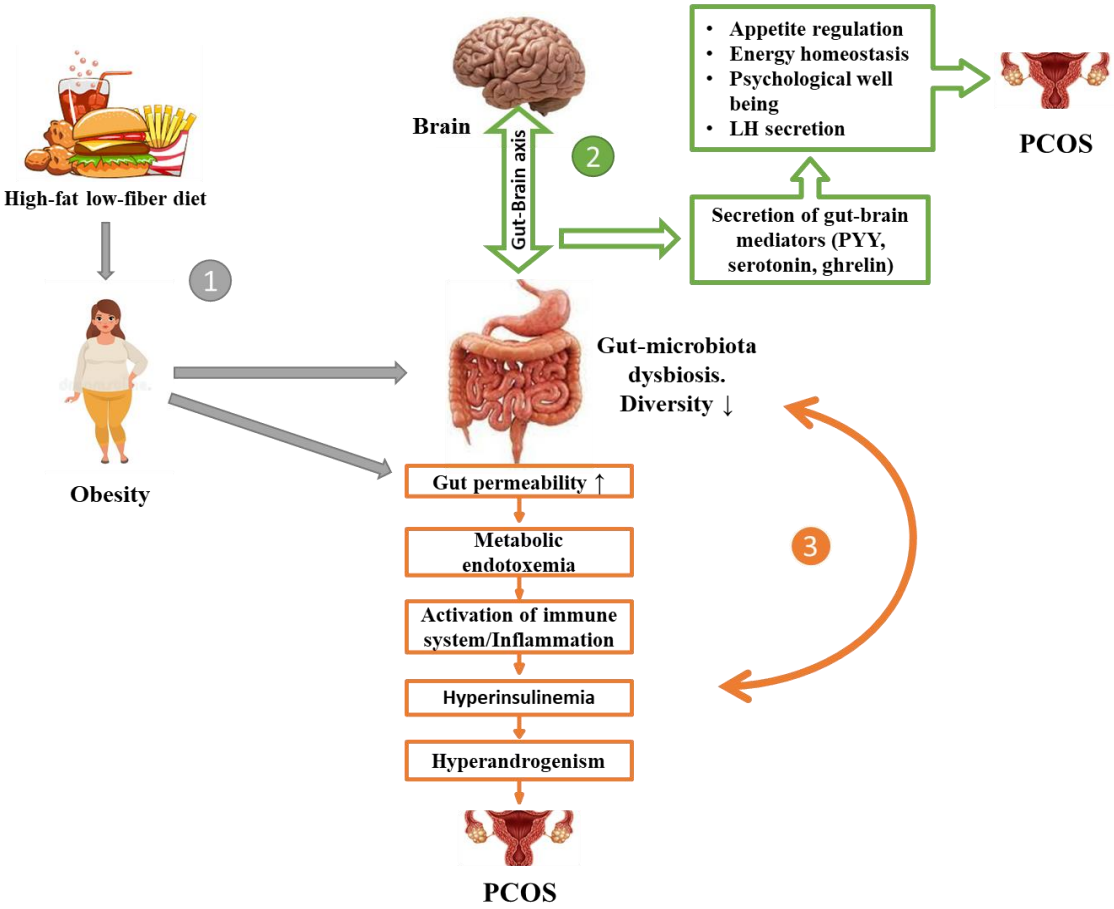

Figure 3: Three possible mechanisms by which gut microbiota may play a role in PCOS pathogenesis.[8]

the gut microbiota causing hyperinsulinemia and insulin resistance. The brain-gut axis is the connection between the gastrointestinal system and the central nervous system. Some of the brain-gut axis mediators e.g., ghrelin, serotonin, and peptide YY (PYY), have been reported to be useful in energy homeostasis, appetite regulation, and LH secretion.[15] These mediators are useful in the regulation of appetite and provide psychological well-being to PCOS-afflicted women. Clostridial bacteria are involved in the biosynthesis of serotonin, while intestinal microbiota producing short-chain fatty acids (SCFAs) have been reported to regulate PYY secretion.[16] However, there are limited no. of studies supporting the relation between PCOS pathogenesis and gut-brain mediators (Figure-3).

Furthermore, it has been proposed that androgens might contribute to the development of PCOS. Recent research has linked alterations in the gut flora of PCOS women to hyperandrogenism. However, there has been very little research examining the association between gut microbiome and sex steroids. Sex hormones may have an immediate effect on gut microbiota composition by modifying energy production and beta-glucuronidase activity, or they may have an indirect effect by activating steroid receptors in the host.[10]

Role of Probiotics, prebiotics, and synbiotics; New treatment approach in PCOS

As PCOS is a highly complicated and multifactorial condition, no single known treatment can be offered to every patient. Traditional treatment is medical care that focuses on each person's symptoms. In the first step, it is recommended to make changes to lifestyle, such as losing weight by eating less and working out. When changing a person's lifestyle isn't enough to control the symptoms, they are given medical treatment to help them feel better. Mostly, people take oral anti-diabetes medicines and oral contraceptives. However, if a woman with PCOS takes oral contraceptives for a long time, she may gain weight and have problems with her metabolism. Furhermore, ovulation-inducing drugs can cause multiple follicles to grow and release eggs, which can lead to more than one pregnancy. Also, this method does not affect the symptoms of hyperandrogenism.[8]

What are probiotics?

The term "probiotics," which refers to living organisms that are not known to cause disease in hosts and have beneficial effects on those hosts, originates from a Greek word that translates to "for life".[17] Lilly and Stillwell defined the term as "*a product produced by one microbe that encourages the growth of another bacteria"*. Later, Fuller broadened the concept to include *"non-pathogenic bacteria that, when ingested, have a beneficial effect on the host's health or physiology"*. The FDA and WHO's most recent definition is "live microorganisms that give health benefits to the host when delivered in adequate amounts".[4]

Probiotics support the immune system, lower blood pressure, control weight, and serum lipids, and treat inflammatory bowel disease and lactose intolerance, as well as autoimmune disorders.[18] Probiotics are widely used to maintain intestinal health by improving the balance of microbiota within the body. The gut microbiota is thus brought into balance by a rise in beneficial bacteria that flourish in an acidic environment and a decrease in harmful bacteria that cannot survive in such an environment.[8]

Natural sources

Probiotics are naturally present in many food sources, yogurt being the most common source. Other food sources include kefir, ayran, pickles, tarhana (sundried tomato, yogurt, and flour), turnips, wine, beer, soy products, olives, bacon, and dried or fermented meat products,are examples of foods that naturally contain probiotic microbes.[8]

Major probiotics used in PCOS

Two genera of lactic acid-producing bacteria, *Lactobacillus* and *Bifidobacterium*, are the most used in the control of PCOS.[14] Other species used to control PCOS include *Streptococcus*, *Lactococcus*, and *Saccharomyces*. Several subspecies of *Lactobacillus* and *Bifidobacterium* are used for the management of PCOS including *L. reuteri, L. acidophilus, L. plantarum, L. fermentum, L. casei, L. bulgaricus, L. rhamnosus, L. delbruekii, L.* salivarius, *B. breve, B. longum, B. bifidum, B. infantis, and B. lactis* are the most commonly used probiotics. Of all the strains, *L. plantarum HL2, L. plantarum CCFM1019*.[19] *B. bifidum, and B. longum HB3* have been reported to be the most useful probiotics for PCOS control.[14]

Role of probiotics supplementation on PCOS

Different studies have shown that probiotic supplementation positively impacts PCOS-affected women's metabolic profiles. A randomized, double-blind trial showed a decline in the fast plasma glucose levels, the concentration of serum insulin, triglycerides, and homeostatic model assessment of insulin resistance (HOMA-IR) through the probiotic supply for 12 weeks in the PCOS-affected women.[20]

According to another triple-blind RCT, the treatment by probiotics combined with vitamin D increased the levels of GSH and TAC significantly and lowered the amounts of TT and MDA by treating them with *L.acidophilus* for 12 weeks.[21]

There isn't much research examining how probiotic supplementation affects PCOS-afflicted women's hormonal profiles. According to research by Karamali *et al*., 2018 probiotic supplementation (*L. acidophilus, L. casei*, and *B. bifidum*) for 3 months enhanced plasma total antioxidant capacity and sex hormone binding globulin (SBHG) in PCOS-affected women and lowered blood testosterone levels when compared to the control group.[22] In a different study, fecal microbiota transplantation and treatment with *Lactobacillus* for PCOS were linked to lowered blood testosterone levels, elevated estrogen levels, and regular menstrual cycles.[13] Administration of probiotics may enhance total testosterone, and SHBG through better insulin sensitivity, decrease the production of pro-inflammatory cytokines and raise fecal pH.[23]

A recent study evaluating the effect of multi-strain probiotics combined with lifestyle modifications showed significant improvement in menstrual irregularity, testosterone levels, and menstrual domain of quality of life.[24] Zhang *et al.,* 2019 studied the impact of *B. lactis V9* on gut-brain mediators, sex hormones, and the intestinal microbiome. They found that levels of LH and FSH were decreased while there was a notable increase in sex hormones and intestinal SCFAs.[25] A study examining the effect of 8 lactic-acid-producing bacteria on letrozole-induced rats demonstrated significantly effective results. *L. plantarum* HL2 restored the levels of testosterone, LH, and FSH. *B. longum* HB3 showed decreased testosterone levels and improved ovarian abnormalities.[26]

In short, we can conclude from this data that probiotics can be efficient supplementation to lifestyle as well as dietary interventions in PCOS-afflicted women. However, more studies are required to have a clear idea of strain-specific mechanisms and to know which probiotics do not contribute to the control of the condition.

The beneficial effect of probiotics can be explained by various potential mechanisms. In addition to balancing the gut microflora, there are numerous mechanisms of action of probiotics summarized in the figure below. It is worth mentioning that probiotics are very strain-specific in their action and characteristics (Figure-4). Effectiveness and the mode of action for every strain or combination of strains are very different and cannot be extrapolated to other strains.[27]

Prebiotics

Prebiotics are typically defined as "nondigestible food components that are resistant to the action of hydrolytic enzymes at the top of the GIT, transit into the colon in the unmodified state, and benefit the host organism's microflora by selectively boosting the growth and/or activity of one or a limited number of bacteria in the colon, hence improving host health".[5]

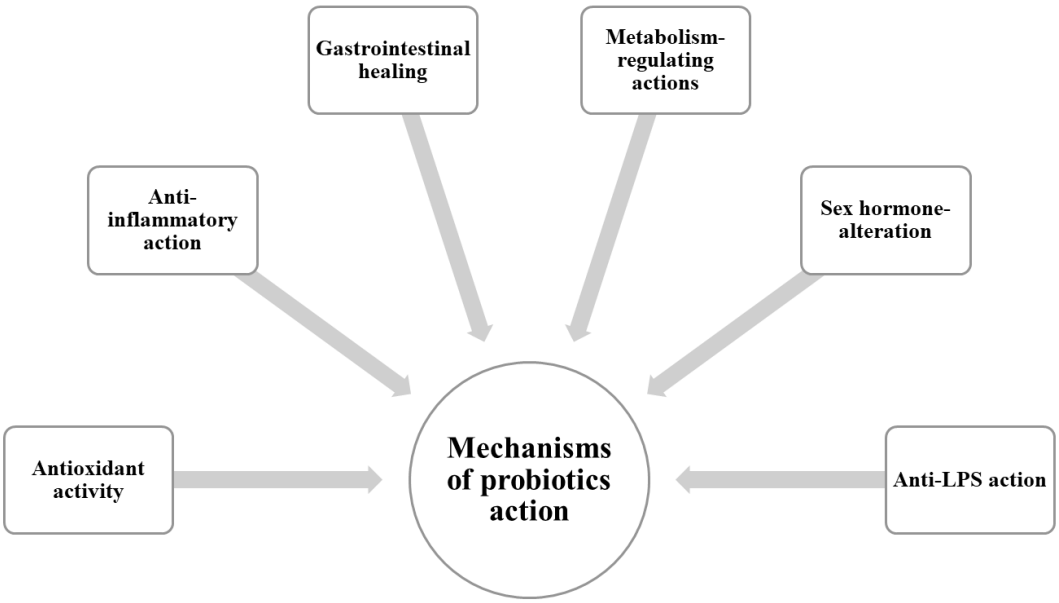

Figure 4: Mechanisms of probiotic action that may help understand their beneficial role in PCOS.

Prebiotics can improve the health of the host in several ways including; increased bifidobacteria, pathogen growth inhibition, immune system modulation, rotavirus inhibition, stimulation of intestinal microflora activity, treatment of diarrhea and irritable bowel syndrome, prevention of intestinal inflammation and cancer, intervention in lipid metabolism, etc. Inulin, resistant dextrin, oligofructose, fructooligosaccharide, galactooligo-saccharide, and lactulose are examples of prebiotics.[18]

Natural sources

Natural foods like leeks, asparagus, artichokes, garlic, onions, wheat, oats, and bananas contain prebiotics. Prebiotics can also be found in breast milk, soybeans, inulin-rich foods (such as chicory roots, Jerusalem artichokes, and unrefined barley), yacon, and non-digestible carbohydrates, particularly non-digestible oligosaccharides.[29]

Role of prebiotics supplementation on PCOS

Prebiotics modify the microbiota's makeup, which has a favorable impact on metabolic indicators. The supplementation of prebiotics is connected to the considerable increase in plasma gut peptide concentrations and a decrease in levels of hunger. There are many positive effects of prebiotics on health through various metabolic pathways.[4]

There could be the promotion of the development of both *Bifidobacterium* and *Lactobacillus* by prebiotics. Fermentation of these bacteria results in the production of SCFAs such as propionate, acetate, etc. Therefore, prebiotics chiefly increase both blood glucose and blood lipid profile.[28]

Women with PCOS who took prebiotic supplements (20 g resistant dextrin) for three months showed significant improvements in HDL cholesterol levels as well as significant reductions in fasting plasma glucose, hs-CRP, serum TG, total cholesterol, and LDL cholesterol. According to this study, resident dextrin used by women with PCOS may reduce testosterone levels, hirsutism, and irregular menstrual cycles.[18] It should be noted that altered microbiota composition as a result of prebiotics has yet to be investigated. Therefore, it's unclear if the minor effects are the result of altered gut flora.[8]

A study evaluating the effect of inulin, fructooligosaccharides, and *L. acidophilus* on body weight, blood metabolites, and lipid profile of PCOS rats found that the 10-week treatment notably decreased blood glucose level and body weight. As for the lipid profile, there was a decrease in overall cholesterol, triglycerides, and LDL levels.[29]

Inulin and metformin have been reported to alleviate PCO morphology in rats by anti-inflammatory activity and gut microbiota modulation. The dose of 21 days, it was observed that metformin and inulin supplementation reduced the body weight and total testosterone levels. Inflammatory indicators (TNF-α, IL-6, and IL-17A) were also reported to be decreased while the treatment promoted the growth of *Bifidobacterium*.[30]

Synbiotics

Foods or other items that contain probiotics as well as prebiotics are referred to as synbiotics. The combinations of *Bifidobacterium* + FOS, *Lactobacillus* + lactitol, and *Bifidobacterium* + GOS are the most well-known synbiotics. Synbiotics are believed to be very useful for improving the metabolic profile as they help produce SCFAs and reduce the expression of inflammatory genes.[8] A synbiotic product benefits the host by increasing survival rates and implanting living microbial dietary supplements in the digestive system. To achieve this, one or a limited number of health-promoting bacteria are targeted for growth and/or metabolism activation.[17]

Role of synbiotic supplementation on PCOS

In one study, it was revealed that after 8 weeks of consuming synbiotic pomegranate juice and synbiotic beverages by women with PCOS, insulin sensitivity rose, although BMI, body weight, and waist circumference values remained unchanged.[31] Another RCT evaluating the effect of synbiotic supplementation (*L. acidophilus, L. casei, L. bulgaricus, L. rhamnosus, B. longum, B. breve, Streptococcus thermophilus*, and prebiotic Inulin (fructooligosaccharide) on lipid profile and anthropometric indicators showed a reduction in LDL levels and increase in HDL levels. As lipid profile is a common issue in PCOS, this study showed that symbiotic supplementation could reduce the disease symptoms.[32]

A recent double-blind, placebo-controlled study on PCOS women evaluating the effect of synbiotics and lifestyle modifications showed a considerable decrease in testosterone levels (32%) in the synbiotic group than in the placebo group (6%). The decrease in BMI was observed to be 5% in the placebo group along with a considerable reduction in the thigh circumference, hip, and waist. The symbiotic group experienced a decrease of 8% in BMI in addition to a decrease in thigh circumference, waist, and hip.[33] In a meta-analysis, symbiotic supplementation for women with

Table: Different studies assessing the impact of pro, pre, and symbiotic supplementation in PCOS women.

Author, year, reference	*Country*	*Study design*	*Intervention*	*Species (dosage)*	*Duration*	*Intervention (n)*	*Control (n)*	*Main findings*
Ahmadi *et al*, 2017[20]	Iran	Single-blind RCT	Probiotic	*L acidophilus* (2×10^9 CFU/g), *L casei* (2×10^9 CFU/g), *B bifidum* (2×10^9 CFU/g)	12 weeks	30	30	↓weight, ↓BMI, ↓FPG, ↓insulin, ↓HOMA-*β*, ↓HOMA-IR, ↓QUICKI, ↓TG, ↓VLDL
Xiaoxia *et al.,* 2020[21]	China	Triple-blind RCT	Probiotic	*L acidophilus* (5×10^6 CFU/g)	12 weeks	30	30	↑GSH, ↑TAC, ↓MDA, ↓TT
Karamalli *et al*., 2018[22]	Iran	Double-blind RCT	Probiotic	*L acidophilus* ($2x10^9$ CFU/g), *L casei* ($2x10^9$ CFU/g), *B bifidum* ($2x10^9$ CFU/g)	12 weeks	30	30	↑TAC, ↓SHBG, ↓total testosterone, ↓MDA, ↓mF-G scores, ↓hsCRP
Shamasbi *et al.,* 2018[18]	Iran	Triple-blind RCT	Prebiotic	Resistant dextrin (20 g)	12 weeks	31	31	↓FPG, ↓hs-CRP, ↓TG, ↓total cholesterol, ↓LDL, ↑HDL, ↓DHEA-S, ↓free testosterone
Masroor et al., 2019[29]	Pakistan	Double-blind RCT	Prebiotic	Inulin (5% w/w), fructooligosaccharide (5% w/w) and L1 (1% *L. acidophilus* w/w about 1×10^{10} CFU/g)	10 weeks	27	18	↓weight, ↓blood glucose, ↓triglycerides, ↑HDL, ↑LDL
Esmaeilinezhad *et al.,* 2019[31]	Iran	Triple-blind RCT	Synbiotic	SPJ group: 2 L/wk pomegranate juice containing 20 g inulin + $2x10^8$ CFU/g Lactobacillus PJ group: 2 L/wk of pomegranate juice SB group: 2 L/wk of beverage containing 20 g inulin + $2x10^8$ CFU/g Lactobacillus + pomegranate flavoring	8 weeks	69	23	↓BMI, ↓weight, ↓waist circumference, testosterone, ↓insulin, ↑insulin sensitivity in SPJ and SB group, ↔FPG, ↔LH, ↔FSH
Karimi *et al.,* 2020[32]	Iran	Double-blind RCT	Synbiotic	*L acidophilus* strain T16 (IBRCM10785), *L casei* strain T2 (IBRCM10783), *B bifidum* strain T1 (IBRC-M10771) ($2x10^9$ CFU/g) + 800 mg inulin	12 weeks	30	30	↓Insulin, ↓HOMA-IR, ↑QUICKI, ↓TG, ↓VLDL, ↔FPG, ↔total cholesterol, ↔HDL, ↔LDL

PCOS has shown a great improvement in indices of insulin resistance, which is a major contributor to PCOS, thus improving the symptoms of the condition.[34]

Because the preparation of every symbiotic is unique, having different strains of probiotics and different prebiotic compounds, each preparation needs to be separately assessed for its effectiveness in PCOS management and its mechanism of action since it is possible that all of the synbiotic preparation will not be effective.

However, synbiotics have been suggested to be a promising treatment agent for PCOS.[35]

Table is a summary of studies that looked at the effects of probiotic, prebiotic, and synbiotic supplements on women with PCOS.

Conclusion and Recommendations

Based on reviewing studies, this systematic review concluded that probiotics, prebiotics, and synbiotics are potential treatments for PCOS, targeting its diverse and complex pathophysiology. Consumption of pro, pre, and synbiotics can significantly reduce the metabolic and hormonal markers of the condition. Probiotics, like *Lactobacillus* and *Bifidobacterium*, improve insulin sensitivity, lower inflammation, and reduce fasting insulin levels. Prebiotics encourage gut flora development and short-chain fatty acid synthesis, promoting hormonal balance. Synbiotics combine probiotics and prebiotics to enhance hormonal and metabolic processes.

The use of pro, pre, and synbiotics by women suffering from PCOS has shown significant improvements in the symptoms of the condition. However, the number of studies assessing the effect of probiotics, prebiotics, and synbiotics in PCOS women is limited. Therefore, further large-scale clinical trials are needed to identify the best strains, doses, and treatment durations. Future research should consider unique microbiome profiles and PCOS characteristics to optimize treatment efficacy and ensure long-term safety.

Conflict of interest: None declared.

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