

Probiotic Interventions for Polycystic Ovarian Syndrome – A Comprehensive Review

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DOI: [10.36348/sijog.2024.v07i06.001](https://doi.org/10.36348/sijog.2024.v07i06.001)

Received: 07.04.2024 | Accepted: 11.05.2024 | Published: 01.06.2024

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Abstract

Polycystic ovarian syndrome (PCOS) is a complex endocrine disorder characterized by hormonal dysregulation, metabolic disturbances, and reproductive abnormalities. Probiotics are the gut bacteria which helps in digestion and possess several functionalities positively in body like immunomodulation, hormonal balancing, antihypertensive etc. There are evidences pointing for preventive as well as therapeutic results from the PCOS symptoms by administering probiotics to the adolescent women. Some triggers causing implications of gut microbiota alterations in PCOS, including modulation of host metabolism, inflammation, insulin resistance, and reproductive function. Present paper reviews the mechanism through which these outcomes are achieved.

Keywords: PCOS, Probiotic, Insulin resistance, Hyperandrogenism, Gut microbiota.

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1. INTRODUCTION

Polycystic ovarian syndrome (PCOS) represents one of the most common endocrine disorders affecting women of reproductive age, with an estimated prevalence of 6% to 12% worldwide [1]. In 2017, 1.55 Million (95% UI: 1.19–2.08) incident cases of PCOS among women of reproductive age (15–49 years) were reported globally [2]. This multifaceted condition is characterized by a constellation of symptoms, including menstrual irregularities, hyperandrogenism, and polycystic ovarian morphology on ultrasound examination [1]. Importantly, PCOS is not solely confined to reproductive issues but often entails various metabolic disturbances, such as insulin resistance, dyslipidaemia, and obesity, thereby predisposing affected individuals to long-term health risks, including type 2 diabetes mellitus, cardiovascular disease, and infertility. In present review the intervention of probiotics with the restoration capabilities for PCOS is reviewed in detail.

2. Polycystic Ovarian Syndrome

The term ‘Stein–Leventhal syndrome’ has already been used to name PCOS for decades. [3] Stein and Leventhal provided the first description of PCOS as the combination of hirsutism (a condition of male-

pattern terminal hair growth in women), amenorrhoea (absence of menstruation), chronic anovulation and infertility, obesity and enlarged cystic ovaries. However, it was not until 1990 that the WHO included ‘E28.2 Polycystic ovarian syndrome’ — with sclerocystic ovary syndrome and Stein–Leventhal syndrome as synonyms — among the disorders of ovarian dysfunction included in the International Classification of Diseases, 10th revision (ICD10) [4]. With the ability to measure hormone concentrations, the diagnostic criteria were revised to include inappropriate gonadotropin secretion and hyper-androgenemia. Development of ultrasonography shifted attention to ovarian morphology. However, with recognition of the role of insulin resistance/hyperinsulinemia in PCOS, the development of methods to measure insulin sensitivity in vivo, and awareness of the higher risk of these patients for abnormalities of carbohydrate metabolism, and possibly cardiovascular complications, focused attention on the metabolic abnormalities of the disorder [3] Overall the accepted criteria for defining PCOS are NIH, ESHRE/ ASRM and Rotterdam which include following phenotypic characteristics.

PCOS is a heterogeneous disorder of mysterious aetiology. The definitions mentioned in

Table 1 require exclusion of specific disorders that might have signs and symptoms that overlap with those of PCOS, such as non-classic congenital hyperplasia, hyperprolactinaemia, thyroid dysfunction, hypercortisolism and androgen-secreting tumours [4]. Many features have been associated with the disorder, like ovulatory dysfunction, polycystic ovaries on either ultrasonographic or histopathological examination, hirsutism, hyperandrogenaemia, abnormal gonadotrophin concentrations, and most recently insulin resistance and hyperinsulinemia. The proceedings from an expert meeting held in May 2003 in Rotterdam recommended that PCOS be defined, when at least two of the following three features were present, after exclusion of other aetiologies: oligo- or anovulation, clinical and/or biochemical hyperandrogenism, or polycystic ovaries. However, these newer criteria effectively create additional phenotypes of PCOS e.g. women with hyperandrogenism and polycystic ovaries but normal ovulatory function, and women with

ovulatory dysfunction and polycystic ovaries but no clinical or biochemical evidence of hyperandrogenism [5].

2.1. Etiology of PCOS

Etiology of PCOS remains incompletely understood, a combination of genetic predisposition, environmental factors, and lifestyle influences is thought to contribute to its development [5]. In addition to the criteria explained in Table 1, recently accepted pathophysiological mechanisms have been implicated in PCOS, including [1]-

- a. Hormonal imbalances,
- b. Insulin resistance and metabolic dysregulation,
- c. Chronic low-grade inflammation, and

Understanding these underlying factors is crucial for elucidating the intricate pathogenesis of PCOS and identifying potential therapeutic targets is summarised in Fig. 1.

Table 1: PCOS defining criteria according to NIH & Rotterdam conferences [3, 4]

Defining Criteria	Inclusions	Exclusions
Child Health and Human Disease (NICHD) of NIH, 1990	1. Hyperandrogenism and/or hyperandrogenemia 2. Oligo-ovulation or Menstrual dysfunction	Ovarian etiology and/or consequences.
sponsored in part by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) Rotterdam, 2003	1. Oligo- or anovulation 2. Clinical and/or biochemical signs of hyperandrogenism 3. Polycystic ovaries	
Androgen Excess and PCOS Society (AE-PCOS), 2006	Hyperandrogenism, Ovarian dysfunction and/or PCOM	
National Institute of Child Health and Human Development	Presence of both hyperandrogenism and ovulatory dysfunction but	Ovarian morphology

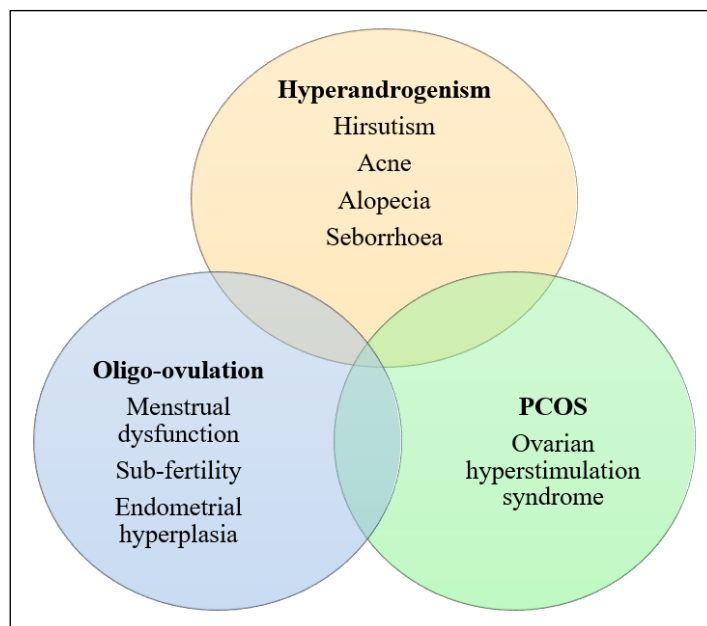


Fig. 1: Phynotypic charecteristics of PCOS

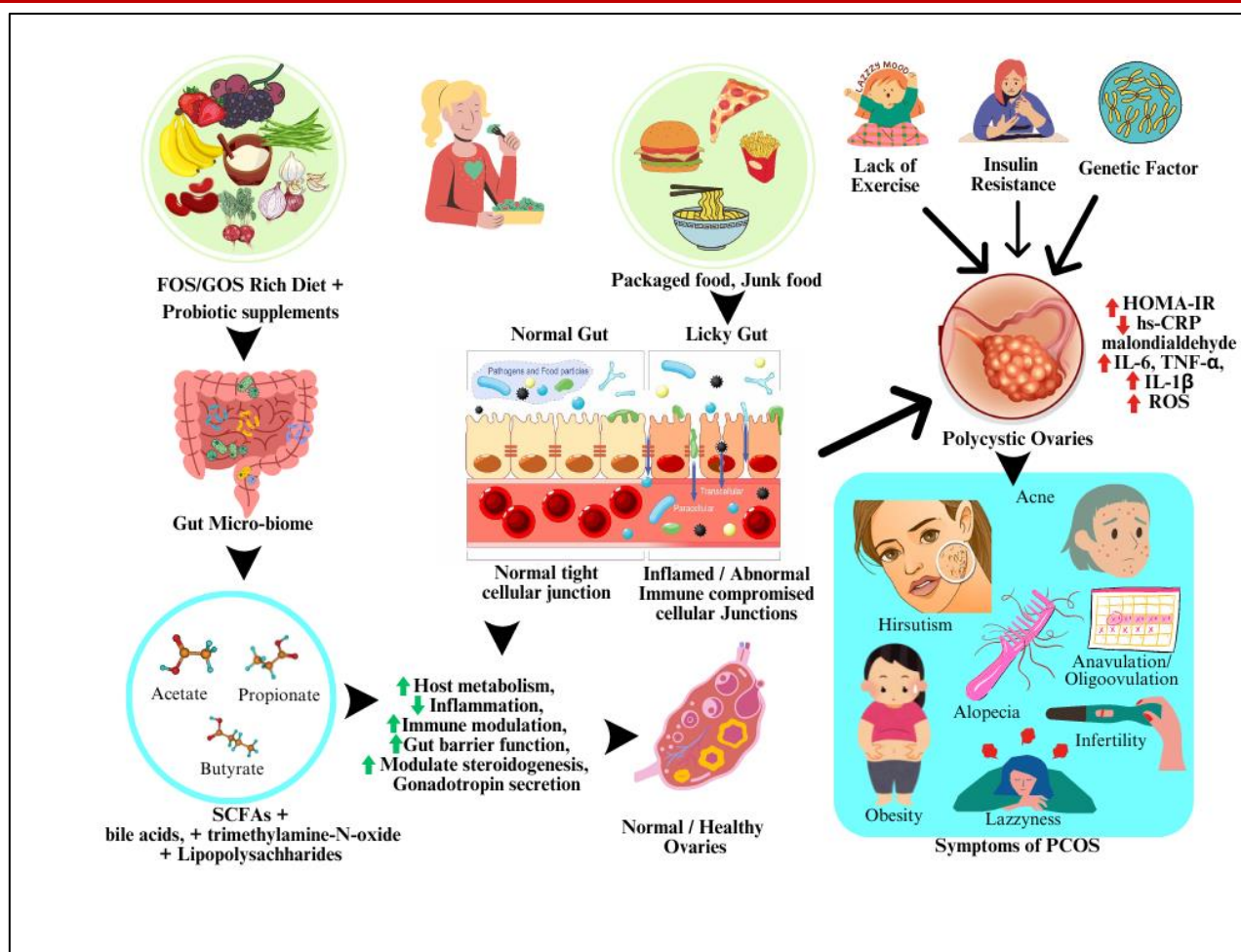


Fig. 2: Pharmacological summary of PCOS association with Probiotics

a. Hormonal Imbalances in PCOS

One of the hallmark features of PCOS is hormonal dysregulation, characterized by elevated levels of androgens, particularly testosterone, and luteinizing hormone (LH), and disrupted follicle-stimulating hormone (FSH) secretion [6]. This dysregulation disrupts the delicate balance between the hypothalamic-pituitary-ovarian (HPO) axis, leading to anovulation, menstrual irregularities, and follicular arrest [7]. Hyperandrogenism, manifested as hirsutism, acne, and alopecia, is a common clinical manifestation of PCOS and contributes to the pathogenesis of reproductive dysfunction and metabolic disturbances observed in affected individuals. Furthermore, aberrant steroidogenesis, impaired insulin signalling, and dysregulated gonadotropin secretion further exacerbate hormonal imbalances in PCOS, perpetuating a vicious cycle of endocrine dysfunction [8].

b. Insulin Resistance and Metabolic Dysregulation

Insulin resistance, defined as impaired tissue responsiveness to insulin action, is highly prevalent in PCOS and contributes to hyperinsulinemia, compensatory hyperglycaemia, and dyslipidaemia [1]. Hyperinsulinemia exerts direct and indirect effects on ovarian function, promoting androgen synthesis,

inhibiting sex hormone-binding globulin (SHBG) production, and disrupting follicular development and ovulation. Moreover, insulin resistance exacerbates adipose tissue dysfunction, leading to increased adiposity, adipokine dysregulation, and chronic low-grade inflammation, further amplifying metabolic dysfunction in PCOS.

c. Role of Inflammation in PCOS

PCOS is characterized by increased circulating levels of proinflammatory cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF- α), and elevated markers of systemic inflammation, including C-reactive protein (CRP). This inflammatory milieu not only exacerbates insulin resistance and dyslipidaemia but also disrupts ovarian function, impairing follicular maturation and steroidogenesis.

2.2. Current Therapeutics for PCOS

Despite of high prevalence and clinical significance, the management of PCOS remains challenging, primarily due to its heterogeneous presentation and complex underlying pathophysiology [6]. There is no drug or treatment for PCOS exists. Current treatment strategies primarily focus on alleviating symptoms and mitigating long-term health

risks. Targets for pharmacological treatment might include androgen excess, oligo-ovulation and insulin resistance, but lifestyle counselling should be provided in all cases in order to prevent or treat obesity are mentioned in Table 2 [4, 7, 8]. Nevertheless, a substantial

proportion of PCOS patients may experience suboptimal response or intolerable side effects with conventional therapies, highlighting the urgent need for alternative, more effective treatment modalities.

Table 1: Pharmacological targets in PCOS & treatments available[3], [4]

Pharmacological Target	Clinical Signs/ Symptoms	Treatment depending on their severity and their psychological repercussions			
		Cosmetic methods/ dermo-cosmetics	Topical Drugs for non-conceiving Women	Orla Administration non-conceiving Women	Other
Androgen excess	Hirsutism	Bleaching, plucking, shaving, waxing, chemical treatment, photo epilation and electrolysis	Eflornithine	Progestin, Cyproterone, Chlormadinone, Drospirenon, Neutral progestin (Contraceptive) Cyproterone acetate (androgen receptor blockers) Spironolactone or Flutamide and 5 α -reductase inhibitors	Diet, Exercise
	Acne	Dermabrasion, laser or light therapy or cosmetic surgery for severe scarring,	Retinoids		
	Alopecia	Hairstyling, Hair replacement and additions, hair transplantation, growth factors from platelet-rich plasma or stem cell-based therapies	Minoxidil		
Oligo-ovulation	Infertility	-	-	Metformin, Clomiphene citrate or Letrozole	Diet, Exercise, Leproscopic surgery
Anovulation	Infertility	-	-	Metformin, Clomiphene citrate or Letrozole	Diet, Exercise, Leproscopic surgery
Polycystic Ovaries	Multiple cysts	-	-	progestin (Contraceptive)	Leproscopic surgery
Insulin resistance	Diabetes Mellites / Diabetes Type II	-	-	Metformin, Thiazolidinediones, Berberine or Inositols, Incretin-based therapies	Diet, Exercise,

3. Probiotics

All mammals, including humans, lives along with a large and varied population of different microorganisms which reside in their intestine as an ecosystem. According to the Food and Agriculture Organization/World Health Organization guidelines, probiotics are live microorganisms which, when administered in adequate amounts, confer health benefits on the host'[9]. The term "probiotic" was first used in 1965, by Lilly and Stillwell, to describe substances secreted by one organism which stimulate the growth of another. Nowadays, probiotics represent an important group of beneficial consumed/supplemental microorganisms that can live in foods/supplements and

in the intestine [9]. The gut microbiota, comprising trillions of microorganisms inhabiting the gastrointestinal tract, plays a pivotal role in host metabolism, immune modulation, and gut barrier function [6]. Probiotics are mainly bacterial strains of the lactic acid bacteria (LAB) Lactobacillus, Bifidobacterium, and Enterococcus and the yeast Saccharomyces. According to Generally Recognised as Safe (GRAS) guidelines probiotics should not cause disease in humans; they should be completely non-pathogenic and should not be able to evolve into pathogenic variants [10, 11].

The zero risk does not exist, and that acceptance of the concept that probiotics may not only have positive effects but potentially also side effects is important. Mild side effects from probiotics in the gastrointestinal tract (GIT) are most common. The symptoms, such as bloating, constipation, flatulence, dyspepsia, nausea, and abdominal discomfort rather do not influence the safety of the probiotic. due to rapid emergence of probiotics as drugs, a harmonized approval process similar to other drugs covering all aspects of Investigational New Drug Application (INDA) and New Drug Application (NDA) has been proposed in which organisms falling under Generally Recognized As Safe (GRAS) category are exempted from INDA submission whereas non-GRAS, GRAE or new organisms are not exempted [12, 13].

4. PCOS and Probiotics Linkage

In recent years, there has been growing interest in the potential role of the gut microbiota and probiotics in the pathogenesis and management of various metabolic and inflammatory conditions, including PCOS [1, 8]. Alterations in the composition and diversity of the gut microbiota, termed dysbiosis, have been implicated in the pathogenesis of metabolic disorders, insulin resistance, and low-grade inflammation observed in PCOS [6]. Probiotics, have emerged as a promising therapeutic strategy for modulating the gut microbiota and ameliorating PCOS-related symptoms [6]. By restoring microbial balance, enhancing gut barrier integrity, and exerting anti-inflammatory effects, probiotics hold potential in addressing the multifactorial nature of PCOS and improving clinical outcomes.

Several mechanisms trigger the implications of gut microbiota alterations in PCOS, including modulation of gut integrity, host metabolism, inflammation, insulin resistance, and reproductive function.

4.1. Gut Integrity

Intestinal dysbiosis may contribute to systemic inflammation and metabolic disturbances through altered gut barrier integrity, increased gut permeability, and dysregulated host-microbe interactions, highlighting the intricate interplay between the gut microbiota and PCOS pathophysiology. In PCOS, alterations in gut microbiota composition have garnered significant attention due to their potential role in the pathogenesis and progression of the disorder. Several studies have reported differences in the gut microbiota profile between women with PCOS and healthy controls, suggesting a potential association between gut dysbiosis and PCOS-related metabolic and reproductive abnormalities. Research exploring the gut microbiota composition in PCOS patients has revealed alterations in microbial diversity, abundance, and functional capacity compared to healthy individuals. Specifically, PCOS patients often exhibit decreased microbial diversity, characterized by reduced richness and evenness of microbial species within the gut ecosystem [14].

In addition to changes in microbial diversity and abundance, dysbiosis in PCOS is associated with gut barrier dysfunction, which may exacerbate metabolic and inflammatory disturbances observed in affected individuals. Dysbiotic alterations in gut microbiota composition can disrupt the integrity of the intestinal epithelial barrier, leading to increased gut permeability and bacterial translocation [15]. Disruption of tight junction proteins, such as occludin and zonulin, compromises the integrity of the gut barrier, allowing the passage of luminal antigens, microbial metabolites, and pathogenic bacteria into the systemic circulation (Tremellen and Pearce 2012). This phenomenon, often referred to as "leaky gut," promotes systemic inflammation, immune activation, and metabolic endotoxemia, contributing to the pathogenesis of PCOS [16].

Moreover, specific alterations in the relative abundance of microbial taxa have been observed in PCOS, with notable changes in the abundance of Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria phyla [17]. In terms of specific microbial taxa, PCOS patients frequently exhibit an overabundance of certain bacterial species associated with metabolic dysfunction and inflammation, such as *Lactobacillus* spp., *Prevotella* spp., and *Ruminococcus* spp. Conversely, beneficial bacteria, including butyrate-producing taxa such as *Faecalibacterium prausnitzii* and *Akkermansia muciniphila*, are often depleted in PCOS patients [15]. Probiotics have been shown to enhance gut barrier function by promoting the expression of tight junction proteins and reducing intestinal permeability. By restoring gut barrier integrity, probiotics may attenuate systemic inflammation and improve insulin sensitivity in PCOS [18]. It improves the nutritional absorption in systemic circulation for their health benefits. Probiotics can restore microbial balance by promoting the growth of beneficial bacteria and suppressing pathogenic microbes [19].

4.2. Microbial Metabolite

Dysbiosis-associated changes in microbial metabolite production, such as SCFAs, bile acids, and trimethylamine-N-oxide (TMAO), can impact host physiology and metabolism, modulating insulin sensitivity, lipid metabolism, and inflammation [16]. Additionally, lipopolysaccharides (LPS), also observed to play pivotal roles in regulating gut barrier function [20].

SCFAs, produced through the fermentation of dietary fiber by gut microbiota, exert beneficial effects on intestinal barrier integrity by promoting mucus production, enhancing tight junction assembly, and modulating immune responses [21]. Conversely, dysbiosis-associated reductions in SCFA-producing bacteria, such as *Faecalibacterium prausnitzii* and *Roseburia* spp., may compromise gut barrier function and exacerbate inflammation in PCOS [22].

Bile acid metabolism can also influence gut barrier integrity and inflammation in PCOS. Bile acids, synthesized in the liver and modified by gut microbiota, serve as signalling molecules regulating intestinal epithelial cell proliferation, mucin secretion, and tighten the cell junction integrity [23]. Dysbiosis-associated changes in bile acid composition and metabolism, characterized by alterations in primary and secondary bile acid profiles, may disrupt gut barrier function and exacerbate metabolic dysfunction in PCOS [24].

Trimethylamine-N-oxide (TMAO)

Lipopolysaccharides (LPS)

4.3. Metabolic Dysfunction:

Dysbiosis-associated changes in gut microbiota composition and metabolism can impact host energy homeostasis, lipid metabolism, and glucose handling, contributing to metabolic dysfunction observed in PCOS. Dysbiotic alterations in microbial taxa, such as decreased abundance of butyrate-producing bacteria and increased prevalence of opportunistic pathogens, may promote insulin resistance, dyslipidemia, and adipose tissue dysfunction [15]. Moreover, dysbiosis-induced alterations in microbial metabolite production, such as SCFAs, bile acids, and TMAO, can influence host metabolism, inflammation, and energy expenditure, exacerbating metabolic disturbances in PCOS [16].

Probiotics may modulate appetite-regulating hormones, such as ghrelin and peptide YY, leading to alterations in energy intake and expenditure. By regulating appetite and energy balance, probiotics may contribute to improvements in insulin sensitivity and metabolic parameters in PCOS [25].

Dysbiosis-associated alterations in bile acid metabolism have been implicated in the pathogenesis of insulin resistance and metabolic dysfunction. Probiotics can modulate bile acid composition and metabolism, leading to improvements in lipid profiles, hepatic steatosis, and insulin sensitivity. By optimizing bile acid metabolism, probiotics may exert beneficial effects on metabolic parameters in PCOS patients [26].

4.4. Chronic Inflammation:

Dysbiosis-mediated disruptions in gut barrier integrity and increased gut permeability can lead to bacterial translocation, systemic inflammation, and immune activation, contributing to the pathogenesis of PCOS-associated inflammation and insulin resistance [20]. Dysbiotic alterations in gut microbiota composition, characterized by increased abundance of proinflammatory taxa and reduced diversity of beneficial bacteria, may exacerbate systemic inflammation, impairing ovarian function, and promoting metabolic dysfunction in PCOS. Chronic low-grade inflammation is a characteristic feature of PCOS and is associated with dysregulated hormone production and insulin resistance. By attenuating inflammation, probiotics may restore normal hormone secretion and improve reproductive

function in PCOS [27]. Furthermore, dysbiosis-induced alterations in immune modulation and inflammatory signalling pathways can perpetuate a proinflammatory state, amplifying the severity of PCOS-related symptoms. Probiotics have anti-inflammatory properties and can reduce circulating levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α). By attenuating inflammation, probiotics may improve insulin sensitivity, lipid metabolism, and other metabolic parameters in PCOS patients [28]. Probiotics have been shown to inhibit the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6), TNF- α , and interleukin-1 beta (IL-1 β), in both in vitro and in vivo studies. By suppressing inflammatory cytokine production, probiotics can mitigate inflammation and its deleterious effects on metabolic and reproductive function in PCOS patients [29]. By promoting an anti-inflammatory immune profile, probiotics may dampen immune activation and reduce inflammation in PCOS. Additionally, probiotics may regulate immune tolerance and prevent autoimmune reactions associated with PCOS [28].

Oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) production and antioxidant defences, contributes to inflammation and metabolic dysfunction in PCOS. Probiotics have antioxidant properties and can scavenge free radicals, reduce ROS production, and enhance antioxidant enzyme activity. By reducing oxidative stress, probiotics may alleviate inflammation and improve metabolic parameters in PCOS patients [30].

4.5. Insulin Resistance

Insulin resistance is commonly associated with hormonal imbalances in PCOS and contributes to hyperandrogenism by increasing androgen production in the ovaries. Probiotics have been shown to improve insulin sensitivity and reduce insulin resistance in both animal models and clinical studies. By enhancing insulin signalling pathways and glucose metabolism, probiotics may indirectly modulate androgen levels and improve hormonal balance in PCOS [31]. Probiotics, particularly certain strains of *Lactobacillus* and *Bifidobacterium*, can ferment dietary fibers to produce SCFAs, which play a crucial role in regulating host metabolism by promoting insulin sensitivity, enhancing glucose uptake in peripheral tissues, and reducing hepatic glucose production thereby improve insulin sensitivity and glucose homeostasis in PCOS patients [19]. Dysbiosis in the gut microbiota can lead to increased gut permeability and bacterial translocation, which contribute to systemic inflammation and insulin resistance.

4.6. Gut-Brain Axis

Probiotics can influence the communication between the gut microbiota and the central nervous system, including the hypothalamic-pituitary-ovarian (HPO) axis. By modulating neurotransmitter production

and signalling pathways, probiotics may regulate gonadotropin-releasing hormone (GnRH) secretion and gonadotropin levels, thereby exerting indirect effects on ovarian hormone production and menstrual cycle regulation [27]. Dysbiotic alterations in microbial metabolite production may disrupt the delicate balance of sex hormone metabolism and signalling pathways, contributing to menstrual irregularities, hyperandrogenism, and impaired follicular development observed in PCOS [23].

Dysbiosis-associated alterations in gut microbiota composition and metabolism may impact reproductive function and hormone regulation in PCOS. Gut microbiota-derived metabolites, such as SCFAs and bile acids, can modulate steroidogenesis, gonadotropin secretion, and ovarian function through direct and indirect mechanisms [21]. By promoting the growth of beneficial bacteria that produce SCFAs, probiotics may indirectly inhibit androgen production in the ovaries and adrenal glands, thereby reducing hyperandrogenism in PCOS [32]. Certain probiotic strains, such as *Lactobacillus* species, have been implicated in the metabolism of estrogen precursors in the gut. By promoting the conversion of estrogen precursors to less active forms, probiotics may help regulate estrogen levels and mitigate estrogen-related symptoms in PCOS, such as irregular menstrual cycles and endometrial hyperplasia [33].

5. Preclinical Trials

Preclinical studies using animal models of PCOS have provided valuable insights into the potential mechanisms and therapeutic effects of probiotic supplementation in PCOS. While research in this area is still emerging, several preclinical studies have demonstrated promising outcomes of probiotic use in improving metabolic parameters, reproductive function, and inflammation in PCOS-like conditions. Some of the preclinical studies supporting probiotic use in PCOS animal models shows positive acceptance for the beneficial effect of prebiotics for the therapeutic benefits in PCOS. Xu *et al.*, (2018) investigated the effects of probiotic supplementation with *Lactobacillus rhamnosus* and *Bifidobacterium longum* on reproductive and metabolic parameters in DHEA-induced PCOS rats. The results demonstrated improved ovarian morphology and restored oestrous cyclicity in PCOS rats. Additionally, probiotic-treated rats exhibited reductions in serum testosterone levels, insulin resistance, and inflammatory cytokine levels compared to untreated PCOS rats [34]. A PCOS-like phenotype was induced in female rhesus monkeys by prenatal androgen exposure to investigate the effects of probiotic supplementation with VSL#3, and a mixture of eight probiotic strains, on metabolic and reproductive parameters in prenatal androgen-treated monkeys. The results showed improved insulin sensitivity and reduced fasting insulin levels in prenatal androgen-treated monkeys. Moreover, probiotic-treated monkeys exhibited improvements in ovarian

morphology and menstrual cyclicity compared to untreated PCOS-like monkeys [35]. According to an experimentation the effects of probiotic supplementation with *Lactobacillus reuteri* on metabolic and reproductive parameters in prenatal androgen-treated mice demonstrated the improved glucose tolerance and insulin sensitivity with probiotic supplementation. Furthermore, the mice exhibited reductions in serum testosterone levels and improvements in ovarian morphology compared to untreated PCOS-like mice [36]. These preclinical studies provide evidence supporting the potential therapeutic effects of probiotic supplementation in PCOS-like animal models. Probiotics have been shown to improve reproductive function, metabolic parameters, and inflammation in PCOS-like conditions, highlighting their potential as a novel therapeutic strategy for PCOS management.

The preclinical studies investigating probiotic use in animal models of PCOS have yielded several key findings and observations like improvement in reproductive function with restoration of estrous cyclicity, improvements in ovarian morphology, and normalization of menstrual cyclicity in probiotic-treated animals compared to untreated PCOS-like animals [34-36].

Metabolic benefits also reported with probiotic supplementation including reductions in serum testosterone levels, improvements in insulin sensitivity, and reductions in fasting insulin levels in probiotic-treated animals compared to untreated PCOS-like animals (Xu and Wu 2018; [35, 36]. Probiotic supplementation has demonstrated reductions in inflammatory cytokine levels and other markers of systemic inflammation [34, 35]. Several studies have reported alterations in microbial diversity, abundance, and functional capacity following probiotic treatment, with shifts towards a more beneficial microbial profile [34, 35]. Restoration of gut barrier integrity, regulation of metabolic pathways, and attenuation of inflammation was also observed [34, 36]. Overall, preclinical studies provide evidence supporting the potential therapeutic benefits of probiotic supplementation as a novel therapeutic strategy for PCOS treatment.

6. Clinical Trials

Clinical studies investigating probiotic supplementation in PCOS patients have provided valuable insights into the potential therapeutic benefits of modulating the gut microbiota in PCOS management. While the research in this area is still evolving, several studies have demonstrated promising effects of probiotics on metabolic parameters, reproductive function, and inflammatory markers in PCOS patients. Samimi *et al.*, performed a randomized, double-blind, placebo-controlled trial to evaluate the effects of probiotic supplementation on metabolic parameters and hormonal profiles in PCOS in 60 patients, who were randomly assigned to receive either a probiotic capsule

containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum* or placebo for 12 weeks. The results showed that probiotic supplementation significantly improved fasting blood glucose levels, insulin sensitivity, and lipid profiles compared to placebo. Additionally, probiotic-treated patients exhibited a reduction in serum testosterone levels and an improvement in menstrual regularity [37].

Another randomized, double-blind, placebo-controlled trial, 60 patients having PCOS were assigned to receive either a probiotic capsule containing *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum* or placebo for 12 weeks. The study aimed to evaluate the effects of probiotic supplementation on insulin resistance and inflammatory markers in PCOS patients. The results demonstrated that probiotic supplementation significantly reduced insulin resistance, as evidenced by improvements in homeostatic model assessment for insulin resistance (HOMA-IR) scores. Moreover, probiotic-treated patients exhibited decreased levels of high-sensitivity C-reactive protein (hs-CRP), indicating a reduction in systemic inflammation [38]. One more randomized, double-blind, placebo-controlled trial investigated the effects of probiotic supplementation on metabolic profiles and hormonal parameters in PCOS patients. Sixty PCOS patients were randomized to receive either a probiotic capsule containing *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum* or placebo for 12 weeks. The results revealed that probiotic supplementation significantly decreased fasting blood glucose levels, insulin resistance, and serum total testosterone levels compared to placebo. Furthermore, probiotic-treated patients exhibited improvements in markers of oxidative stress and inflammation, such as malondialdehyde (MDA) and hs-CRP (Jamilian *et al.*, 2018).

7. Optimising Probiotic Therapy for PCOS

While the precise mechanisms underlying gut microbiota alterations in PCOS remain incompletely understood, potential contributors include hormonal imbalances, dietary factors, lifestyle influences, and genetic predisposition [14]. Strategies targeting the gut microbiota, such as probiotic supplementation, dietary modifications, and fecal microbiota transplantation, represent promising avenues for mitigating metabolic and reproductive dysfunction in PCOS. Overall, probiotics offer a promising approach for reducing inflammation and ameliorating PCOS symptoms through modulation of the gut microbiota, suppression of pro-inflammatory cytokines, enhancement of gut barrier function, reduction of oxidative stress, and modulation of immune responses. Probiotics can restore microbial balance by promoting the growth of beneficial bacteria and suppressing pathogenic microbes [19]. Intestinal barrier dysfunction, characterized by increased gut permeability, allows translocation of microbial products

into the systemic circulation, leading to systemic inflammation.

Strategies targeting the gut microbiota, such as probiotic supplementation, dietary modifications, and fecal microbiota transplantation, represent promising therapeutic approaches for mitigating metabolic and reproductive dysfunction in PCOS. Probiotic therapy holds promise as a complementary approach for managing PCOS; however, several challenges and considerations must be addressed to optimize its efficacy and safety. The challenges and considerations in probiotic therapy for PCOS may include following points:

a. Strain selection and dosing considerations:

- The selection of probiotic strains is critical, as different strains may exert varying effects on gut microbiota composition and host physiology. Strains approved as GRAS and with documented beneficial effects on metabolic parameters and inflammation should be prioritized.
- Optimal dosing regimens need to be established, considering factors such as strain potency, viability, and delivery mechanisms. Dosage may vary depending on the severity of PCOS symptoms and individual patient characteristics.

b. Safety and adverse effects of probiotics:

- Safety profiles of probiotic strains need to be thoroughly evaluated, particularly in vulnerable populations such as pregnant women, children, and individuals with compromised immune function.
- Adverse effects associated with probiotic supplementation, such as gastrointestinal symptoms e.g., bloating, flatulence, diarrhea; allergic reactions, and systemic infections, should be carefully monitored and addressed.

c. Interactions with medications and concomitant therapies:

- Potential interactions between probiotics and medications commonly used to manage PCOS e.g., oral contraceptives, insulin sensitizers etc. need to be considered. Probiotics may influence drug metabolism and bioavailability, impacting treatment efficacy and safety.
- Clinicians should assess potential synergistic or antagonistic effects of probiotics when combined with other dietary supplements or lifestyle interventions commonly used in PCOS management.

d. Heterogeneity of PCOS phenotypes:

- PCOS is a heterogeneous condition with diverse clinical presentations and underlying pathophysiological mechanisms. Probiotic

therapy may need to be tailored to individual phenotypes based on metabolic, hormonal, and inflammatory profiles.

- Stratification of PCOS patients based on specific biomarkers or clinical features may facilitate personalized probiotic interventions and improve treatment outcomes.

e. Standardization of clinical endpoints and biomarkers:

- Standardized criteria for assessing treatment outcomes and defining clinical endpoints are essential for comparing efficacy across different probiotic interventions and study populations.
- Biomarkers reflecting gut microbiota composition, metabolic parameters, hormonal profiles, and inflammatory markers should be included in clinical trials to elucidate mechanisms of action and monitor treatment response.

f. Long-term effects and sustainability:

- Long-term studies are needed to evaluate the sustainability of probiotic effects on gut microbiota composition, metabolic health, and PCOS symptoms.
- Strategies to promote adherence to probiotic therapy and maintain treatment benefits over time should be explored, considering factors such as patient education, lifestyle modifications, and continuous monitoring.

g. Future Directions for research and clinical application:

- Prospective randomized controlled trials with large sample sizes and longer follow-up periods are needed to confirm the efficacy and safety of probiotic therapy in PCOS.
- Mechanistic studies using animal models and in vitro experiments can elucidate the underlying pathways by which probiotics exert beneficial effects on PCOS pathophysiology.
- Integration of multi-omics approaches, including metagenomics, meta-transcriptomics, and metabolomics, can provide comprehensive insights into the interactions between probiotics, gut microbiota, and host physiology in PCOS.

Addressing these challenges and considerations will be essential for advancing probiotic therapy as a viable adjunctive treatment option for PCOS, potentially improving metabolic health, reproductive outcomes, and overall quality of life for affected individuals. Collaboration between researchers, clinicians, and industry stakeholders is crucial for translating scientific evidence into clinical practice and optimizing patient care.

8. CONCLUSION

In conclusion, the exploration of probiotic interventions for PCOS has revealed promising insights into its potential as a complementary therapeutic approach. Key findings from preclinical and clinical studies have demonstrated the ability of probiotics to modulate gut microbiota composition, improve metabolic parameters, reduce inflammation, and alleviate PCOS symptoms. These findings underscore the importance of considering gut microbiota dysbiosis as a contributing factor to PCOS pathogenesis and the potential of probiotics as a targeted intervention. In clinical practice, incorporating probiotic supplementation alongside conventional treatments may offer a novel strategy for enhancing metabolic and reproductive outcomes in PCOS patients. However, several challenges, including strain selection, dosing considerations, safety profiles, and long-term effects, warrant further investigation. Future research directions should focus on elucidating the mechanisms of action of probiotics, conducting well-designed clinical trials with standardized endpoints, and exploring personalized approaches based on PCOS phenotypes. By addressing these considerations and advancing our understanding of probiotic therapy, we can optimize its clinical utility and improve the management of PCOS. However, further research is needed to elucidate the causal relationship between gut dysbiosis and PCOS and to explore the therapeutic potential of modulating the gut microbiota in PCOS management.

Conflict of Interest: Authors report no conflicts of interest.

Declaration: Citation and referencing is managed through an AI Tool.

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