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Assessing How Probiotics, Prebiotics, and Synbiotics Affect Insulin Sensitivity and Endocrine Disturbances in PCOS-Affected Women

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Abstract

The poly cystic ovary syndrome (PCOS) is a highly common endocrine-metabolic condition in women of reproductive age, which involves insulin resistance, hyperandrogenism, and ovulatory malfunction. According to new evidence, there is an involvement of gut microbiota in the pathophysiology of PCOS, and microbiome-oriented therapies are attracting great attention. This systematic review identifies the effectiveness of probiotics, prebiotics and synbiotics in the management of insulin resistance and hormonal dysregulation in women with PCOS, using the randomized clinical trial (RCTs). A large scale of electronic databases was searched to identify relevant RCTs considering metabolic, endocrine outcomes in the context of the microbiome-modulating intervention. It was shown that the markers that probiotic and synbiotic supplementation substantially increased include fasting insulin, HOMA-IR, total testosterone, LH/FSH ratio, and menstrual regularity. Prebiotics were less well studied and had promise. Some of the suggested mechanisms are regulating gut dysbiosis, supporting short-chain fatty acid production, systemic inflammation, and intestinal barrier performance. Although promising, heterogeneity in the study designs, strains, dosage, and treatment duration does not allow making firm conclusions. Additional good-quality, long-term RCTs are needed to validate treatment worth and come up with standard guidelines. However, the introduction of microbiome-directed interventions can be viewed as a new adjunctive approach to metabolic and reproductive outcomes in PCOS in females.

Keywords: ***Polycystic Ovary Syndrome, SGLT2 Inhibitors, Insulin Resistance, Hyperandrogenism, Metabolic Syndrome, Female Reproductive Health, Type 2 Diabetes Mellitus, Endocrine Therapy, Cardiometabolic Risk, Weight Loss Therapy.***

1.Introduction

PCOS constitutes a complex endocrinometabolic dysfunction that inappropriately impacts women of reproductive age. Having an incidence of between 5 and 15 percent globally, it poses as one of the predominant reasons as to why a large number of persons experience menstrual irregularities and infertility and the occurrence of metabolic issues. PCOS is a complicated endocrine pathology that is characterized by a complex interaction of hormonal disorders (hyperandrogenism, chronic anovulation) and metabolic disorders (IR) and marked by the risks of developing type 2 diabetes, dyslipidemia, cardiovascular disease, and psychological disorders. The heterogeneity of the syndrome becomes highlighted by the fact that the syndrome has variable phenotypes, which exhibit a continuum of clinical and metabolic phenotype, and this makes it challenging to diagnose and treat this syndrome. The commonest diagnostic framework is the Rotterdam criteria which requires at least two of the following oligo/anovulation, clinical/biochemical hyperandrogenism, and polycystic ovarian morphology.

Insulin resistance is a key pathological feature of PCOS that is reported to be in up to 75 percent cases, especially when cases are overweight or obese. Hyperinsulinemia worsens androgen excess because it lowers sex hormone-binding globulin (SHBG) levels to elevate free testosterone concentrations in the circulation. Not only does this aggravate dermatological and reproductive symptoms in the form of hirsutism, acne, and infertility, but also leads to a sequence of metabolic impairments(1). Those conventional treatment modalities include use of combined oral contraceptives (COCs) and insulin sensitizing agents such as metformin which are aimed to control the symptoms, but not the disease. Nonetheless, the side effects, possible metabolic imbalances as well as poor compliance make the long-term use of these therapies restrictive. These constraints have led to the consideration of adjunctive and alternative remedies that address the upstream mechanisms of PCOS pathologic processes, including the gut microbiota dysregulation.

Current studies have helped to shine a light on the significance of gut microbiome in the regulation of systemic metabolism, inflammation and balancing of other hormonal states. Women with PCOS have an abnormal

microbial balance in the gut with reduced diversity of the microbiome and an increase in pro-inflammatory bacterial species over anti-inflammatory bacterial species. Dysbiosis is also linked to metabolic endotoxemia; widespread inflammation, impaired glucose metabolism and even neuroendocrine dysfunction through the gut-brain-ovary axis. These realizations have given rise to an increased interest in gut-modulating therapies, that is, probiotics, prebiotics, and synbiotics, as possible non-pharmacologic strategies capable of restoring microbial homeostasis and countering metabolic and endocrine disruption in PCOS.

Probiotics are live microorganisms that when consumed in well amounts provide some health benefit to the host, and they have been found effective in the correction of insulin sensitivity and lipid profiles. Some of the most commonly looked at strains are those belonging to the Lactobacillus and the Bifidobacterium genera and are known to increase the integrity of the gastro buffer, decrease inflammatory cytokines, and alter glucose insulin tolerance. Instead, prebiotics stimulate the development of healthful intestinal microbiota and short-chain fatty acids (SCFAs) production, which regulated the glucose balance and inflammation. Prebiotics are dietary non-digestible fibers. Synbiotics are mixtures of probiotics and prebiotics, and have the theoretical potential to develop synergistic effects, due to enhancement of the survival and performance of microorganisms in the gastrointestinal tract(2).

An ever-increasing number of randomized controlled trials (RCTs) have been conducted investigating the therapeutic potential of such microbiome-based interventions in women with PCOS. The encouraging results are heterogeneous and situational-specific. A number of trials have shown statistically significant positive results in terms of insulin resistance (HOMA-IR), fasting insulin and glucose, lipid profile, and androgen marker such as total testosterone and SHBG. In fact; the synbiotic formulations are observed to have more potent effects with respect to the single application of probiotics or prebiotics, possibly because of greater colonisation by the microbes and synergy of metabolism. The domain is however confined by methodological inconsistencies between studies including difference in strains and erfection of microbe and difference in duration of the intervention and the phenotypes of the participants.

To summarize all the available evidence and present a better picture of the current therapeutic option, this systematic review included the investigation into the effectiveness of probiotic, prebiotic, and synbiotic supplementation among women that were diagnosed with PCOS. The review used only randomized clinical trials and followed PRISMA guidelines; the results were reviewed according to important outcomes connected with insulin sensitivity, hormonal balance, lipid metabolism, and the markers of inflammation. All included studies applied clear diagnostic criteria most of them being that of Rotterdam guidelines and also had interventions that lasted at least 8 weeks which is also appropriate to note significant metabolic changes. The majority of the tests were carried out with overweight or obese women aged 15-48 years, a group that is especially sensitive to metabolic consequences of PCOS disease.

It was found that during the interventions in which synbiotics were used, the effects were consistently associated with the improvement of insulin-related markers and the profile of hormones, that is, the decrease in HOMA-IR, fast glucose concentration, and insulin levels in the circulation and the increase in SHBG and the reduction in a total testosterone amount. The probiotic-only interventions were also found to be effective though to a lesser extent. The use of prebiotics alone was studied less frequently yet demonstrated low to moderate effectiveness in modifying the inflammatory state, namely, a decrease in inflammatory markers and an improvement of lipid profiles. In combination, microbiome-based supplementation adherence was good, and adverse outcomes were few, indicating the safety and tolerability of microbiome-based treatments in this patient group.

Besides positive findings, the review revealed that numerous limitations deter the firm draws. These are small sample sizes, geographic homogeneity (all the studies were carried out in Iran) and absence of long-term follow up. In addition, the lack of standardized formulations and differences in outcome measures cannot support meta-analytic synthesis and reduces research generalizability(3). Future recommendations lie on conducting multicentred and extensive RCT with heterogenous populations and interventions that are strictly controlled. The profile and metabolic analyses of gut microbiota would also be useful to clarify the mechanism of action and phenotype responder.

To sum up, taking probiotic, prebiotic, and synbiotic supplements to be secondarily used in managing metabolic and hormonal disturbances in women with PCOS is an exciting avenue to pursue. These interventions seem to open the path to the era of individualized, microbiota-informed approaches that would deal with the causes of PCOS and not just its symptoms. Further research into this field would be able to revolutionize the treatment of women with this complicated condition and enhance their long-term health state.

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2.Methods

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Insulin resistance is a key pathological feature of PCOS that is reported to be in up to 75 percent cases, especially when cases are overweight or obese(4). Hyperinsulinemia worsens androgen excess because it lowers sex hormone-binding globulin (SHBG) levels to elevate free testosterone concentrations in the circulation. Not only does this aggravate dermatological and reproductive symptoms in the form of hirsutism, acne, and infertility, but also leads to a sequence of metabolic impairments. Those conventional treatment modalities include use of combined oral contraceptives (COCs) and insulin sensitizing agents such as metformin which are aimed to control the symptoms, but not the disease. Nonetheless, the side effects, possible metabolic imbalances as well as poor compliance make the long-term use of these therapies restrictive. These constraints have led to the consideration of adjunctive and alternative remedies that address the upstream mechanisms of PCOS pathologic processes, including the gut microbiota dysregulation.

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TABLE 1 Overview of Methodological Framework for Systematic Review

Category	Description
Review Design	Systematic Review following PRISMA 2020 guidelines; registered in PROSPERO (CRD42024587531)
Databases Searched	PubMed, Scopus, Embase, Web of Science, Cochrane CENTRAL
Search Strategy	Combined MeSH and free-text terms (e.g., “PCOS”, “probiotic”, “HOMA-IR”, “testosterone”) with Boolean operators (“AND”, “OR”)
Eligibility Criteria	RCTs involving women (15–45 years) with PCOS (Rotterdam/NIH/AES criteria), intervention ≥8 weeks, English language, with hormonal/metabolic outcomes
Exclusion Criteria	Non-RCTs, studies without control groups, non-English texts, duration <8 weeks, outcomes limited to reproductive metrics only
Population (P)	Women of reproductive age diagnosed with PCOS
Intervention (I)	Supplementation with probiotics, prebiotics, or synbiotics (capsules, powders, or functional foods)
Comparator (C)	Placebo or standard care
Outcomes (O)	Primary: HOMA-IR, insulin, glucose, SHBG, testosterone. Secondary: lipid profiles, hs-CRP, DHEA-S, apelin, AIP
Screening Process	Two independent reviewers; disagreements resolved with third reviewer; inter-rater agreement measured using Cohen’s kappa ($\kappa = 0.95, 0.90$)
Data Extraction	Standardized form; extracted study design, demographics, intervention details, outcomes, adherence, and adverse events
Risk of Bias Tool	Cochrane RoB 2.0 tool; domains assessed: randomization, allocation concealment, blinding, attrition, reporting bias

It was found that during the interventions in which synbiotics were used, the effects were consistently associated with the improvement of insulin-related markers and the profile of hormones, that is, the decrease in HOMA-IR, fast glucose concentration, and insulin levels in the circulation and the increase in SHBG and the reduction in a total testosterone amount. The probiotic-only interventions were also found to be effective though to a lesser extent. The use of prebiotics alone was studied less frequently yet demonstrated low to moderate effectiveness in modifying the inflammatory state, namely, a decrease in inflammatory markers and an improvement of lipid profiles. In combination, microbiome-based supplementation adherence was good, and adverse outcomes were few, indicating the safety and tolerability of microbiome-based treatments in this patient group.

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To sum up, taking probiotic, prebiotic, and synbiotic supplements to be secondarily used in managing metabolic and hormonal disturbances in women with PCOS is an exciting avenue to pursue. These interventions seem to open the path to the era of individualized, microbiota-informed approaches that would deal with the causes of PCOS and not just its symptoms. Further research into this field would be able to revolutionize the treatment of women with this complicated condition and enhance their long-term health state.

3.Results

In the course of the search, 514 unique records were retrieved by utilizing the five major scientific databases. A total of 418 records after the elimination of 96 duplicate records underwent the screening of titles and abstracts. Of the total, 398 were filtered based on irrelevance or did not fulfil inclusion criteria mostly based on lack of RCT design and lack of reporting of relevant outcomes in the hormonal and metabolic category. After the assessment, 11 randomized controlled trials carried out in 2018-2022 were chosen to conduct a full-text analysis and to be included into the final synthesis. It is worth mentioning that all research papers were carried out in Iran, making demographic patterns uniform yet limiting the possibility of their further application to the general population.

A total amount of participants in all of the trials included was about 420 women with PCOS between the age of 15 and 48 years, with most of them being classified as overweight and obese (BMI 25 kg/m 2 or higher). Standardized baseline in the diagnostic aspect was assured by Rotterdam criteria of diagnosis amongst all participants(8). The methodological reliability was promoted by most trials being either double or triple-blind. The length of interventions was 8 to 12 weeks and the levels of adherence to the studies were high (generally over 90 with little dropout or side effects reported).

In terms of type of intervention, 6 studies employed the use of synbiotics, 3 studies employed the use of probiotics alone and two studies employed the use of prebiotics by itself. The way of delivery was diverse and could be in a form of capsules, sachets, and functional drinks like synbiotic pomegranate juice. Most probiotic formulations included mixtures of Lactobacillus acidophilus, L. casei, L. rhamnosus, Bifidobacterium longum and Streptococcus thermophilus. Prebiotic products usually consisted of inulin, fructo-oligosaccharides (FOS) or dextrin. The dosing varied between 500mg and 2g /day and colony-forming unit (CFU) varied between 10 8 to 10 10 CFU / g of formulation.

3.1 Effects on Insulin Resistance and Glycemic Indicators

In all of the studies under analysis, the effects on parameters linked to insulin resistance, including HOMA-IR, fasting blood glucose (FBS), and fasting insulin, were the most frequent. The study conducted by Esmaeilinezhad et al. (2018) found a combination of synbiotic pomegranate juice to be significantly decreasing the HOMA-IR scores, insulin and glucose levels in comparison with the placebo group and other active comparator groups. Equally, Samimi et al. (2018) managed to observe a significant decrease in fasting plasma glucose and insulin levels and increased insulin sensitivity indices on the 12th week of synbiotic supplementation.

Shoaei et al. (2021), although found no significant changes in primary glycemic indices, demonstrated significant improvement in insulin levels after accounting corrections to baselines in the covariates, so there may be a hidden benefit that needs even more time to become obvious. Appreciable decreases in HOMA-IR and insulinlevels by using synbiotic capsules were demonstrated by Darvishi et al. (2020) in addition to raised HDL cholesterol- which are some additional metabolic advantages.

Synbiotic formulation was solely reported to have the most significant insulin-sensitizing effect especially when the Lactobacillus species and Bifidobacterium species are used in conjunction with inulin or FOS. Comparatively, prebiotic-only interventions, like study by Gholizadeh Shamasbi et al. (2018) reported a minor decrease in fasting glucose and improvement of insulin levels, but fewer than their synbiotic equivalents.

3.2 Hormonal Control and Androgen Markers

The impact of the microbiota-targeted therapy upon the hormonal imbalances such as the total testosterone, SHBG, DHEA-S, and free androgen index (FAI) showed also encouraging results. As an example, Arab et al. (2022) observed high changes in levels of SHBG after probiotic supplementation, and increase in testosterone total and DHEA-S remained not significant. In the same light, Karamali et al. (2018) also witnessed a significant increase in SHBG and declined the total testosterone, which accompanied a decreasing modified FerrimanGallwey (mF-G) hirsutism score, as well as inflammatory biomarkers like hs-CRP.

Nasri et al. (2018) also confirmed these observations by reporting higher SHBG and reduced FAI after treating these patients with synbiotic by lowering the levels of malondialdehyde (MDA) and nitric oxide (NO) that serve as markers of oxidative stress and systemic inflammation. Such studies also indicate that synbiotics can reduce hyperandrogenism not only through direct changes in levels of hormones, but also through the effects of inflammatory and oxidative pathways that further increase androgen production.

On the other hand, probiotic monotherapies showed smaller effects on hormonal outcome, as in the case of Shoaei et al. and Arab et al. thus arguing an additive or synergistic effect of composed probiotic-fermentable fiber substrate (i.e., synbiotics).

3.3 Cardiovascular risk and lipid Profiles

Lipid metabolism was also evaluated in several studies with conflicting but mainly positive results. The research by Esmaeilinezhad et al. (2019) indicated that a synbiotic pomegranate juice resulted in the improvement of triglycerides (TGs), LDL cholesterol, and HDL cholesterol and lower systolic blood pressure (SBP), which also shows cardiovascular benefit. Similarly, Karimi et al. (2020) obtained substantial lowering of LDL and rise in HDL cholesterol in women taking two synbiotic capsules, but the levels of the total cholesterol and triglyceride were constant(9).

TABLE 2 Condensed Summary of Key Results

Study	Intervention	Duration	Key Outcomes
Esmaeilinezhad et al.	Synbiotic Juice	12 weeks	↓ HOMA-IR, ↓ insulin, ↑ SHBG
Shoaei et al.	Probiotic Capsule	8 weeks	↓ insulin (adjusted), no hormonal effect
Samimi et al.	Synbiotic Capsule	12 weeks	↓ insulin, ↓ TGs, ↑ insulin sensitivity
Darvishi et al.	Synbiotic Capsule	8 weeks	↓ HOMA-IR, ↑ HDL
Gholizadeh Shamasbi et al.	Prebiotic (dextrin)	12 weeks	↓ LDL, ↓ testosterone, ↓ inflammation
Karamali et al.	Probiotic + Inulin	12 weeks	↓ testosterone, ↑ SHBG, ↓ hs-CRP

The work done on prebiotic by Gholizadeh Shamasbi also showed auspicious changes of lipid profile with decrease of LDL and total cholesterol and an increment of HDL. In combination with an increase in insulin resistance and androgen markers, they indicate that gut microbiota-based therapies are potentially associated with broad, metabolic effects, in addition to glycemic control.

3.4 Safety, Compliance, and Restrictions

The protocols of supplementation were well followed in each trial with rates usually above 90 percent and its observance by counting the capsules, sending reminders and follow-up sessions. Adverse effects were uncommon and mild in the majority of cases; mild allergies were identified in a single trial as the reason behind the termination of the treatment. The majority of trials were adequately powered and used reliable yet validated scales in terms of measurement of hormones using ELISA and validated indices of insulin resistance (HOMA-IR, QUICKI). Nevertheless, the main limitation was that the study population was homogeneous and trials were done in Iran among overweight or obese women, so it cannot be applied to other ethnic groups or BMI status.

The second limitation was the fact that most studies do not analyze the composition of microbiota. Although the clinical outcomes were disseminated, the lack of profiling of gut flora makes the mechanistic connection between the microbiota modulation and clinical improvements venturing into conjecture. Moreover, the length of interventions was quite brief (812 weeks), which did not allow making any conclusions regarding their effectiveness in the long term or the sustainability of the obtained results.

4.Discussion

The systematic review itself was an assessment of the efficacy of probiotics, prebiotics, and synbiotics in the treatment of insulin resistance and hormonal imbalances in women with Polycystic Ovary Syndrome (PCOS), synthesizing evidence presented by 11 randomized controlled trials. The results validate that microbiota-based therapy, particularly synbiotics, is potentially effective in helping meet major metabolic and endocrine disturbances related to PCOS as an auxiliary treatment(10). The level of effect was different among researches, however, the majority of trials proved statistical- and clinically-significant enhancement in insulin resistance indices, androgen markers, and inflammatory mediators, which is key within the PCOS pathophysiology.

Another trend that was quite evident and hugely impressive was the fact that HOMA-IR and fasting insulin levels improved among the subjects, who received synbiotic supplementation. The hypothesis in these findings is that the physiological manipulation of the composition of the gut microbiota might positively affect the host metabolism, especially insulin signaling. This effect is described by several mechanisms that are proposed. To begin with, synbiotics increase the integrity of the gut barrier and decrease endotoxemia, which decreases systemic inflammation, a major cause of insulin resistance in PCOS. Secondly, they enhance the formation of short-chain fatty acids (SCFAs) particularly butyrate, they enhance insulin sensitivity by modifying the expression of genes in hepatocyte and adipose tissue and muscle. Lastly, changes in microbiota might have direct effects on the gut-brain-ovary axis, neuroendocrine messages involving homeostasis of glycemia and hormones of sexual maturation.

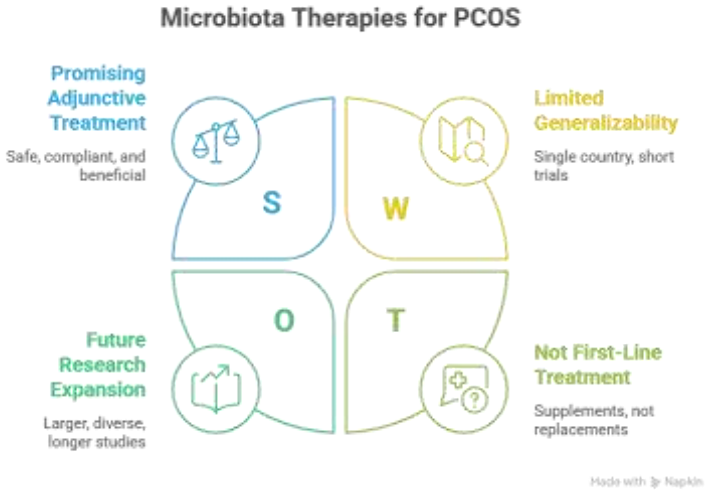

FIGURE 1 Microbiota Therapies for PCOS

Although, in consort, synbiotics performed better than either unilateral probiotic or prebiotic therapy, probiotics in isolation proved effective in reducing fasting insulin and increasing sex hormone-binding globulin (SHBG) although with weaker results. Especially noteworthy is strain-specific benefit of Lactobacillus and Bifidobacterium species. They are said to promote bile acid metabolism, reduce oxidative stress, and initiate the release of GLP-1 which are all positive in the enhancement of insulin action as well as lowering hyperandrogenism. The fact that multi-strain formulations are used throughout trials, however, complicates the possibility of assigning benefits to individual bacterial strains, which is another area of future effort.

Less commonly studied, but also metabolically and hormonally beneficial prebiotic interventions, especially those which improved lipid profiles and lowered markers of inflammation including hs-CRP. These findings support the importance of fermentable dietary fibers in promoting microbial diversity and microbial activity. Notably, prebioitics are selective sources of growth probiotic strains and as such they may find most application in synergistic products as is the case with the synbiotic studies.

The microbiota therapies had a potentially-promising heterogeneous impact on testosterone, SHBG, and DHEA-S through the endocrine perspective. Various trials have indicated the remarkable decreases in the total testosterone levels and elevations in the SHBG, which are essential to alleviate the clinical manifestations, i.e. the hirsutism, acne, and ovulatory impairment. In combination with the effects on insulin dynamics these hormonal alterations hint to the larger systemic balancing effect attributed to gut health. Additionally, decrease in the levels of oxidative stress such as malondialdehyde (MDA) and nitric oxide (NO) were noted in various studies which lead to the conclusion that microbiota-specific interventions have a multi-axes effect which includes immune, metabolic and endocrine axes.

Even though these results are very encouraging, various methodological limitations do not provide broad generalizability and meaning of the findings. The first fact is that all the representative research was published in one country (Iran), and such persons are rather homogenous in terms of ethnics and demographics. Such geographical clustering casts doubt on whether such interventions would show similar outcomes in more diverse cohorts given the documented geographical, dietary and genetic variation in the composition of the gut microbiota.

Second, most trials were relatively short-lived (812 weeks), and there may not be a full assessment of long-term sustenance of benefits or some delayed action on ovulatory cycling, regulation of menstruation, or fertility outcome.

Moreover, microbiome sequencing or profiling were used in very few trials and restrict the mechanistic insight. Learning which subset of bacterial taxa vary in response to interventions and which of these taxa vary most closely with clinical outcomes would be decisive to treatment mechanism questions. Furthermore, none of the investigations studied individual microbiome outcomes, and there is developing knowledge demonstrating that the composition of the baseline microbiome has a large impact on the effect of probiotics. In the future, approaches that combine metagenomics, metabolomics and personalized effect may be able to deliver more versatile, precision-driven microbiome intervention in PCOS.

It is also necessary to mention, that although microbiota-based therapy demonstrated positive outcomes, it was primarily adopted as an addition to the regular care but not its replacement. None of the studies pitted these supplements against first-line treatments using pharmacological medicines, such as metformin, or oral contraceptives. In that regard, the supplements are promising but their usability as individual treatments are still hypothetical. Nevertheless, considering that they do not pose many side effects, are highly compliant, and likely to benefit several pathologies related to PCOS, these therapies can be helpful add-ons or alternatives to sensitive patients to pharmacological practice.

Safety and tolerability were also maintained in favorable way in the trials with no severe adverse outcomes reported. It proves the plausibility of integrating synbiotics into the everyday life of PCOS women with no major risk. The compliance was high as the greatest majority of the participants adhered to supplementation periods using capsules or beverages. Noteworthy, it increases the clinical relevance of these interventions to the real-life clinical context due to its patient-friendly profile.

With these findings, it is apparent that there is a strong need to carry out bigger and multicentric tests using varied populations, more extended follow up as well as better microbial considerations. These articles ought to further stratify outcomes based on PCOS phenotype (e.g. lean vs obese, hyperandrogenic vs normoandrogenic) in order to answer the question of which group benefits more or less, based on a particular intervention. Further, the optimal integrative treatment strategies can be defined through head-to-head tests of the products namely probiotics, prebiotics, and synbiotics-in combination with lifestyle or pharmacologic agents or interventions-ideally.

To sum up, the microbioma-regulating treatments, especially synbiotics, have potential in relieving insulin resistance and hormonal imbalance in PCOS. Although there is existing evidence about them as safe and effective adjunctive interventions, additional studies are indispensable to stipulate formulations, discover responder profiles, and cultivate long-term results. Gut health is an innovative, biologically plausible, and patient-centered way of undertaking a therapeutic idea in dealing with PCOS as a complicated illness because it will provide a reprieve to the patients who are burdened with the disorder.

5.Conclusion and Future work

The present systematic review synthesizes novel evidence on the therapeutic potential of microbiota-specific interventions viz. probiotics, prebiotics and synbiotics regarding their efficacy to overcome insulin resistance and hormonal disturbances in women suffering Polycystic Ovary Syndrome (PCOS). The conclusions that are based on the review of eleven randomized clinical trials state that the supplements of this category should become an effective addition to the management of the metabolic and endocrine dysfunctions at the core of the PCOS pathology. The review supports the increasing scientific evidence that gut microbiota is important in host metabolism, immune modulation and hormonal regulation the processes of which are all derailed in PCOS.

Of all the interventions examined, synbiotics (a combination of both probiotics and prebiotics) showed the most stable and solid effects. In several trials, synbiotic supplement reduced the values of HOMA-IR, fasting insulin, fasting blood glucose, and improved insulin sensitivity scores, including QUICKI, significantly. Moreover, similar interventions and positive effects in the concentrations of sex hormone-binding globulin (SHBG) and total testosterone were also noted, which are an indicator of the improvement of androgenic profiles, a characteristic feature of PCOS. Simultaneously, there was also a decrease in inflammatory factors, such as C-reactive protein (CRP), and indicators of oxidative stress, malondialdehyde (MDA), indicating general metabolic changes positively affecting the patient. The results emphasize the prospects of microbiome-based methods to bring out a multi-dimensional effect on PCOS symptoms and pathology.

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Probiotics alone interventions were also found to have beneficial effects, but overall they were of smaller size than those of synbiotics. The least examined was prebiotics alone but even these had some positive effects, especially as a decrease in LDL cholesterol and systemic inflammation. All these findings can substantiate the idea that gut-directed therapies can adapt the local gastrointestinal processes as well as peripheral endocrine and metabolism axes, most likely by the means of SCFA formation, gut-brain interaction, and enhanced intestinal permeability, and decreased endotoxemia. Nonetheless, the inconsistency in strains of probiotic supplements applied, type of prebiotics, dose and formulations between studies explains the need to have standardized and strain-specific studies.

Though these results are encouraging, there are a number of limitations that need to be addressed before the concept of microbiota-oriented treatment could be implemented as part of the universal PCOS management. To begin with, there was a lack of geographic variations since all the studies used were carried out in Iran. Although this homogeneity offers cultural and nutritional consistency, it restricts the applicability of the studies on other different populations whose gut microbiota may vary due to ethnicity, diets, environment, and genes. Second, the intervention periods are short (with the majority being 8-12 weeks), which does not allow to investigate the sustainability and long-term effects of such interventions. PCOS is a life-long disease, so it is not known that microbiota-based interventions can cause lasting changes or avert long-term complications like diabetes or cardiovascular disease.

The absence of microbiome profiling of studies in the majority of trials was another crucial restriction. The effects on the clinical and biochemical levels were best described, yet there were minimal studies regarding how the composition of the gut microbiome altered with the interventions. Such mechanistic connection is not in place, and it is challenging to assess which exactly bacterial taxa or functional pathways cause the observed effects. Future studies would be enhanced greatly by the addition of sequencing of the gut microbiota, fecal metabolomics or functional microbiome, making interpretation easier and more translable.

The results also indicate a prospects of unexploited ability to achieve personalized supplementation based on the baseline profile of microbiota in the gut of an individual. Recent findings in the study of the microbiome have demonstrated that host-bacteria dynamics are highly diverse and one person may not react the same way as his counterpart to the new probiotic strain implemented based on the microbial presence they already carry. The approach of one size fits all might not be the best one. The future of research may promote precision microbiome treatments potentially modulated by stool testing or algorithms with the help of the machine learning process to align certain strains or formulations to each microbial and clinical phenotype.

Based on the clinical application point of view, these interventions seem to be patient-friendly, highly tolerated and safe. Serious adverse events did not occur in any of the included studies or were low in general. Synbiotics do not have any side effects like those of pharmacological drugs, like metformin or oral contraceptives, which can trigger gastrointestinal discomfort or cardiovascular conditions, meaning that they can be easily included in the diets of most people. They are especially attractive in integrative modes of care due to their simplicity and accessibility.

However, one should point out that microbiota-based therapies should be considered as complementary methods, but not the alternative to first-line treatment. Probiotics or synbiotics cannot be proposed as a specific treatment of PCOS due to the lack of evidence at this moment. Nevertheless, their potential of addressing insulin resistance, lowering systemic inflammation, and toning hyperandrogenism may have potential to increase the efficacy of the pharmacologic interventions or a choice among the women intolerant of drugs or who prefer more natural solutions.

The prospective route has to be well-powered, multi-centre and long-timed studies and, ideally, ethnically and geographically heterogeneous populations involved, by both researchers and clinicians. These experiments ought to be of synbiotics against metformin in combination with lifestyle interventions and in different phenotypes of PCOS (e.g., lean and obese, insulin-resistant and non-insulin-resistant). A more clinical applicability of these findings would be further enhanced by incorporation of longitudinal follow up and fertility-related outcomes (e.g. ovulation rate, pregnancy outcomes).

To sum up, this systematic review underlines the therapeutic prospect of probiotics, prebiotics, and synbiotics in regulating the main metabolic and hormonal imbalances in PCOS. Of these, synbiotics prove the most consistent and multi-dimensional of benefits. Although the evidence is sufficient to conclude that they are a safe and helpful adjunct therapy, additional high-quality research is needed to make favourable formulations, elucidate mechanisms

and determine long term results. With a recent resurgence of concern over the role the gut microbiome plays in the pathogenesis of PCOS, and with biological plausibility to support the effect on PCOS patient outcomes, intervention of the gut microbiome is a new and valid means of achieving holistic and patient-centered care at the prescriptive level. These therapies can become more central in the treatment of this multipronged and multifaceted disorder as we gain a better understanding of it and as tools are refined to allow us to manipulate microbiomes at the individual level.

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Conflicts of interest

The authors have no conflicts of interest to declare

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