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REVIEW

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Symbiotic supplementation: adjuvanted therapy for the treatment of insulin resistance in woman with polycystic ovary syndrome

Suplementação de simbióticos: terapia adjuvante no tratamento da resistência insulínica em mulheres com síndrome do ovário policístico

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Abstract

Introduction: *The chronic inflammatory state and also the hormonal changes caused by Polycystic Ovary Syndrome (PCOS) are factors that, added to insulin resistance and compensatory hyperinsulinemia, may complicate the condition of these patients. On the other hand, studies indicate that the use of symbiotics, including probiotics and prebiotics, can reduce glycemic indexes and insulin resistance.* ***Objective:*** *The present review aimed to analyze previous works investigating the symbiotic capsules usage for improving insulin profile, inflammatory factors, and oxidative stress biomarkers in patients with PCOS.* ***Methods:*** *This review selected five main articles found in Scielo, PubMed, and Google Academic databases.* ***Results:*** *it was clear the benefits of the use of symbiotics in reducing insulin resistance, serum insulin levels, plasma glucose, QUICK, and HOMAR-IR indexes, and apelin-36.* ***Conclusion:*** *supplementation with symbiotic capsules supports beneficial evidence for the treatment of PCOS and should be considered as an adjuvant therapy option, once it helps the prognosis of this disease.*

Keywords: *Polycystic ovary syndrome, Symbiotics, Microbiota, Insulin resistance, blood glucose*

Resumo

Introdução: *O estado inflamatório crônico e as alterações hormonais causadas pela Síndrome do Ovário Policístico são fatores que, somados à resistência insulínica e a hiperinsulinemia compensatória, complicam ainda mais o estado dessas pacientes. Por outro lado, estudos indicam que o uso de simbióticos – probióticos e prebióticos - podem reduzir os índices glicêmicos e a resistência insulínica.* ***Objetivos:*** *analisar artigos prévios que investigassem o uso de cápsulas simbióticas para a melhora do perfil insulínico, fatores inflamatórios e biomarcadores de estresse oxidativo em pacientes com SOP.* ***Material e Método:*** *Esta revisão selecionou cinco artigos principais encontrados nas bases de dados Scielo, PubMed e Google Acadêmico.* ***Resultados:*** *Evidenciou-se o benefício do uso de simbióticos na redução da resistência insulínica, níveis de insulina sérica, glicose plasmática, índices QUICK e HOMAR-IR e apelina-36.* ***Conclusão:*** *A suplementação com cápsulas simbióticas sustenta evidências benéficas para o tratamento da SOP e deve ser considerada uma como opção de terapia adjuvante, uma vez que auxilia no prognóstico dessa afecção.*

Palavras-chave: *Síndrome do ovário policístico, Simbióticos, Microbiota, Resistência à insulina, Glicemia*

Introduction

Polycystic Ovary Syndrome (PCOS) is an endocrinopathy quite frequent in women of reproductive age[1], characterized by the Rotterdam criteria in the presence of at least two of three characteristics: clinical and/or laboratory hyperandrogenism, oligomenorrhea, and sonographic morphology of ovarian polycytosis[2-3]. Currently, the syndrome is considered a cardiovascular risk factor and may increase by up to seven times the chance of a cardiac event due to the high prevalence of metabolic disorders[4], i.e., insulin resistance and hyperinsulinemia, present in approximately 43% of patients with PCOS[5].

The complexity physiopathology of PCOS includes the presence of several biochemical and genetic mechanisms[1]. Previously studies describe that the primary defect consists of insulin resistance in the muscle and adipose tissue, causing compensatory

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hyperinsulinemia, even if the ovaries remain sensitive to insulin. About the resistance, on the other hand, it seems to be related to intrinsic pancreatic beta-cell dysfunction[6]. Consequently, insulin resistance and hyperinsulinemia are associated with chronic inflammation, hormonal changes, follicular dysplasia, endometrial receptors changes, abortion, and infertility, in addition to the psychological impact and increased risk of complications through pregnancy[7].

Although not incorporated into the diagnostic criteria, insulin resistance is present in 50% of women diagnosed with PCOS, regardless of obesity. This condition plays a fundamental role in the production of excess androgens and inhibits the hepatic synthesis of SHBG, increasing the blood concentrations of free testosterone, indirectly interfering in follicular development[8]. Thus, hirsutism, acne, alopecia, possible inhibition of ovarian follicle growth and development, and the development of endometrial disorders occur[7].

The microbiota, known as the "second genome," is a combination of microorganisms that reside commensally with the human intestinal tract[9]; it is estimated that there are 10^{14} microorganisms/ml in the luminal contents, with over 5000 bacteria[10]. As long as this evidence shows that increased cellular inflammatory stress can lead to insulin resistance and that the microbiota interacts with environmental factors and genetic susceptibility, predisposing to the development of other metabolic diseases[11], a hypothesis called DOGMA (Dysbiosis of Gut Microbiota) was proposed to clarify the three main components of the pathogenesis of PCOS. As a result of microbiota dysbiosis in this condition[10], obesity or hyperinsulinemia, fats, and low-fiber foods may result in an unbalance intestinal flora, thus generating destruction of the connection between the intestinal epithelial cells, responsible for the increased permeability of the intestinal mucosa.

In addition, the leaky gut syndrome causes increased permeability of liposaccharides into the systemic circulation, leading to activation of the immune system. This, sequentially, interferes in insulin receptor function, causing insulin resistance. Furthermore, it has been suggested that the gut microbiota causes endotoxemia capable of activating inflammatory activities, leading to obesity and insulin resistance[11] by activating inflammatory mediators such as lipopolysaccharides (LPS), branched-chain amino acids (BCAA), and toll-like receptors (TRL4) which reduce insulin sensitivity[7].

Besides, there is a trend in the study of intestinal bacteria, in which researchers have performed the sequencing, classification, identification, and quantification of the diversity of the microbiota community to individualize the treatment of PCOS, detecting specific bacteria that impact the development of this disorder. Considering this background, it was realized that bacteria from the ***lactobacilli*** and ***bifidobacteria*** families, beneficial for immunity and nutrient absorption, are significantly decreased in women with PCOS, demonstrating a close relationship between intestinal flora and the development of inflammatory diseases such as PCOS. Once the fact that the intestinal flora can regulate insulin synthesis and secretion, as well as influence androgen metabolism and follicular development was confirmed, new symbiotic treatments were proposed as adjuvants to metformin, the therapeutic drug of choice, associated with healthy lifestyle guidance[7].

The term probiotic refers to a supplement composed of live microorganisms that beneficially affect the body by improving the balance of the microbiome[12]. While prebiotics are substances that are not digested and absorbed in the small intestine, but upon reaching the colon, selectively stimulate a bacterium or group of bacteria of the microbiota, providing benefits to the host. Symbiotics, on the other hand, are products that simultaneously present prebiotics and probiotics in their formulation[13]. It is worth noting that probiotic supplements are influenced by the initial dose, quality, temperature, and anaerobic storage conditions[14].

Probiotics, prebiotics, and symbiotics in the form of food supplements became attractive for consumption due to their extra dietary benefit in insulin resistance, obesity, and inflammation, presenting the potential for reducing signs and symptoms of PCOS[15]. Thus, the object of the study of this review was the symbiotic supplementation in women with PCOS, encompassing probiotics and prebiotics, capable of modulating the intestinal flora concerning inflammatory factors and biomarkers of oxidative stress in patients with insulin resistance[16].

Objective

To investigate the use of symbiotics in the treatment of patients with Polycystic Ovary Syndrome, as well as to analyze its impacts and possible benefits on insulin resistance, suggesting alternative therapeutic possibilities for this condition.

Methods

This study consists of a systematic literature review that aims to gather similar ones and analyze about benefits of the usage of symbiotics in the treatment of insulin resistance in PCOS patients. About databases, PubMed, Scielo, and Google Scholar were searched for eligible articles, consulting the following keywords and their combinations in Portuguese and

English: ''probiotics", "Polycystic Ovarian Syndrome", "symbiotics", "glycemia" and "insulin resistance".

The inclusion criteria for the selection of relevant studies included those that addressed insulin resistance in women with PCOS and that presented intervention with probiotic and/or prebiotic capsules without the addition of other components. Furthermore, publications in English and Portuguese were included and also those indexed and published in the databases in the last ten years.

To determine the validity of this review, studies that approached the use of symbiotics in the treatment of PCOS in genetically modified animals; added compounds to the intervention other than the symbiotic capsule; considered PCOS by other criteria than the Rotterdam and that did not specifically analyze the insulin resistance and glycemia of those women was excluded. However, any researches that did not comply with the inclusion criteria, such as publication time and language, were not eligible.

The selection and evaluation of the searched articles were structured in three stages: in the first, the titles of potentially relevant studies to this review were read and those that did not fit any of the previously decided inclusion criteria or that were selected but duplicated were excluded. In the second step, the abstract and introduction of each article were read, and those that met the inclusion criteria were chosen. In the last step, all relevant studies were read, evaluated, checked for eligibility and research relevance using the JADAD and Newcastle Ottawa Scale. This analysis and integration of the articles were analytically performed, resulting in the studies that make up the present systematic review.

Finally, the PICO strategy (Table 1) was adopted as an acronym for Patient, Intervention, Comparison, and Outcomes to address the "guiding question", as well as the delineation of possible hypotheses and methodologies. Since this work is a systematic literature review based on previous publications and evidence presented in the cited platforms, the study in question does not investigate patients directly, and the approval of the Research Ethics Committee was not required. In addition, the paper analyses do not consider exploratory, and also the predeclared primary and secondary endpoints of this research do not changed during this research.

From the pre-defined databases, in the first phase of article selection, 178 citations were found. After the screening process of titles and abstracts and the exclusion of duplicate articles, 16 articles were selected for full-text reading. Finally, 11 studies were excluded due to the incompatibility of the chosen methodology. Thus, according to the inclusion and exclusion criteria, 5 articles were included for the qualitative analysis, which was selected for critical evaluation, analysis, and data extraction (Figure 1).

Results

'Samimi et al (2018)[17] selected sixty women for twelve weeks and half of the volunteers received capsules containing ***Lactobacillus acidophilus strain*** (2×10^9 CFU/g), ***Lactobacillus casei strain*** (2×10^9 CFU/g) and ***Bifidobacterium bifidum strain*** (2×10^9 CFU/g) added to 800 mg inulin and the other half received placebo. When compared to placebo, symbiotic supplementation significantly reduced both serum

Table 1

PICO

P – Population	*I - Intervention*	*C - Comparison*	*O - Outcomes*	*References*
72 Participants with PCOS, aged 18-40 years old Exclusion criteria were: chronic heart, kidney, liver, lung, or pancreatic disease especially cardiovascular diseases, thyroid disorder, small bowel syndrome, autoimmune disease, allergy to probiotic capsules or placebo, use of chemotherapy, corticosteroid, antibiotic, multivitamin-mineral supplements, and omega-3 medications and having specific diet or physical activity programs.	Participants were randomly allocated to one of the two groups: (1) probiotic supplement, (2) placebo, the probiotic group received one probiotic capsule (500 mg) and the placebo group received the placebo daily for 8 weeks.	The probiotic capsule contained the following bacterial strains: ***Lactobacillus casei*** 7×109 CFU/g, ***Lactobacillus acidophilus*** 2×109 CFU/g, ***Lactobacillus rhamnosus*** 1.5×109 CFU/g, ***Lactobacillus bulgaricus*** 2×108 CFU/g, ***Bifidobacterium breve*** 2×1010CFU/g, ***Bifidobacterium longum*** 7×109 CFU/g, ***Streptococcus thermophiles*** 1.5×109 CFU/g and the placebo that contained starch and maltodextrins but no bacteria.	An 8-week multispecies probiotics supplementation had a non-significantly beneficial effect on pancreatic β-cell function and CRP in PCOS patients. After adjustment for some covariates, serum insulin changes were significantly different between groups.	[17]

Table 1

PICO

P – Population	*I - Intervention*	*C - Comparison*	*O - Outcomes*	*References*
88 Participants with PCOS aged between 19 and 37 years and BMI ≥25 kg/m2.	The participants were randomly assigned to receive either active treatment with symbiotic or a placebo. The patients were given 6-week supplement capsules. In the next follow-up visit (end of 6 weeks), the patients were given another set of capsules.	Each symbiotic capsule (500 mg) contained seven strains of beneficial bacteria (***Lactobacillus acidophilus*** 3 ×1010 colony-forming units (CFU)/g, ***Lactobacillus casei*** 3 ×109 CFU/g, ***Lactobacillus bulgaricus*** 5 ×108 CFU/g, ***Lactobacillus rhamnosus*** 7 ×109 CFU/g, ***Bifidobacterium longum*** 1 ×109 CFU/g, ***Bifidobacterium breve*** 2×1010 CFU/g and ***Streptococcus thermophilus*** 3 ×108 CFU/g), prebiotic inulin (fructooligosaccharide), and capsules containing starch and maltodextrin, but no bacteria were used as placebo.	A 12-week symbiotic supplementation has no significant beneficial effects on HOMA-IR and CRP in PCOS patients, whereas the level of apelin 36 significantly decreased.	[18]
60 Participants with PCOS that were diagnosed according to the Rotterdam criteria, aged 18-40 years. Pregnant women, hyperandrogenism, and/ or anovulation, Cushing's syndrome, androgen-secreting tumors, hyperprolactinemia, and thyroid dysfunction, were excluded	Participants were randomized into two groups to receive either one symbiotic capsule (n=30) and placebo (n=30) per day for 12 weeks	Symbiotic capsule containing ***Lactobacillus acidophilus*** strain T16 (IBRC-M10785), ***Lactobacillus casei*** strain T2 (IBRC-M10783), and ***Bifidobacterium bifidum*** strain T1 (IBRC-M10771) (2×109 CFU/g each) plus 800 mg inulin and the placebo that contained starch but no bacteria	Symbiotic supplementation for women with PCOS for 12 weeks had beneficial effects on markers of insulin resistance, triglycerides, VLDL-cholesterol concentrations, and AIP, but did not influence other lipid profiles.	[14]
60 Participants with PCOS, aged 18-40 years old with a BMI greater than 19 kg/m.	Participants were randomly allocated into two treatment groups to intake either probiotic supplements (n=30) or placebo (n=30) for 12 weeks. Every 4 weeks, participants were given enough supplements at least 3 days after their next scheduled visit and were instructed to return all unused supplements at each visit.	The probiotic capsule consisted of three viable and freeze-dried strains: ***Lactobacillus acidophilus*** (2×109 CFU/g), ***Lactobacillus casei*** (2×109 CFU/g), and ***Bifidobacterium bifidum*** (2×109 CFU/g) and a placebo capsule that contained starch but no bacteria.	We found out that probiotic supplementation among PCOS women for 12 weeks had favorable effects on weight loss, markers of insulin resistance, triglycerides, and VLDL-cholesterol concentrations.	[15]
A total of 68 obese or overweight patients (20-44 years old) with PCOS.	A total of 34 people in the symbiotic group received a symbiotic supplement and 34 people in the placebo group received a placebo, daily for 8 weeks. Fasting blood specimens, anthropometric measurements, and dietary intake data were gathered three times during the study.	34 women from the placebo group received a placebo, daily for 8 weeks.	Symbiotic supplementation improved glycemic indexes, lipid profile, and obesity values in women with PCOS. These beneficial effects were not related to alterations in serum apelin levels.	[19]

insulin concentrations (- 2.8 ± 4.1 vs. + 1.8 ± 6.4 μIU/mL, P = 0.002) and insulin resistance (- 0.7 ± 1.0 vs. + 0.4 ± 1.5, P = 0.002), in addition to detecting a significant elevation in the quantitative insulin sensitivity check index (+ 0.01 ± 0.01 vs. - 0.01 ± 0.03, P <0.001).

Karimi E. et al (2018)[15] conducted a study re-

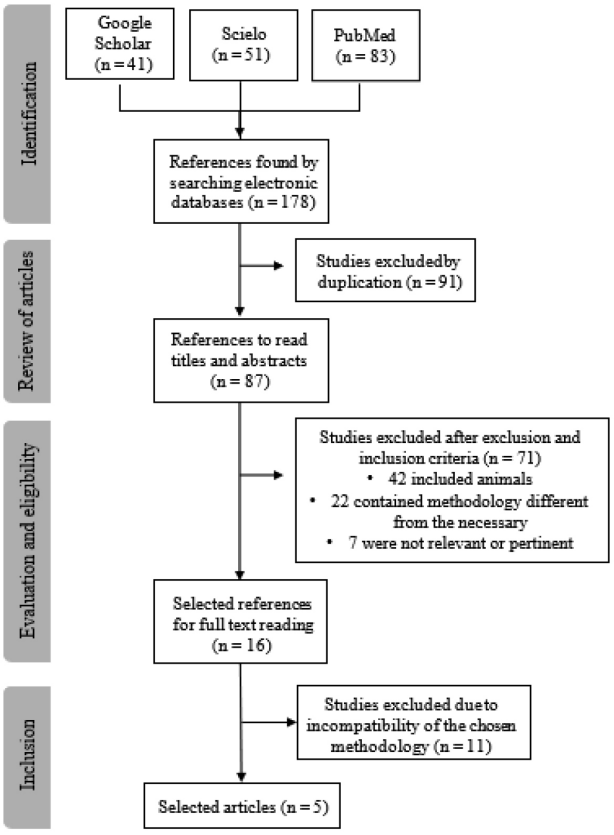

Figure 1 - Flow of information through the different phases of a systematic review

garding the effects of symbiotic supplementation on metabolic parameters and apelin 36 in women with PCOS. In this setting, eighty-eight women were randomly assigned to two groups, an intervention group (n=4) that received capsules containing ***Lactobacillus acidophilus*** 3×10^{10} colony forming units (CFU)/g**,** ***Lactobacillus casei*** 3×10^{9} CFU/g, ***Lactobacillus bulgaricus*** 5×10^{8} CFU/g**,** ***Lactobacillus rhamnosus*** 7×10^{9} CFU/g, ***Bifidobacterium longum*** 1×10^{9} CFU/g, ***Bifidobacterium breve*** 2×10^{10} CFU/g, ***Streptococcus thermophilus*** 3×10^{8} CFU/g) and probiotic inulin (fructooligosaccharide), while the other received a placebo for twelve weeks. A significant difference in apelin 36 after the intervention was observed in the symbiotic and placebo groups (-4-05; 95 % CI -7-15, -0-96, *P=0-004*). However, supplementation with symbiotic capsules showed no benefit in HOMA-IR index, QUICKI, and CRP in overweight or obese patients with PCOS, even with the reduction in apelin 36 blood concentration decreasing from 27 (sd 21) nmol/l at the onset to 14.4 (sd 4-5) nmol/l after three months, compared with the increase in the placebo group with onset from 26 (sd 15) nmol/l after three months to 18.4 (sd 2-9) nmol/l. Finally, there was also no benefit in HbA1c and two-hour fasting glucose (PGF2h).

Ahmadi et al (2017)[18] evaluated the effects of probiotic supplementation on weight loss, blood glucose and lipid profile in women with PCOS through a randomized, double-blind clinical trial in which thirty women received a capsule consisting of ***Lactobacillus acidophilus*** (2×10^{9} CFU/g), ***Lactobacillus casei*** (2×10^{9} CFU/g), and ***Bifidobacterium bifidum*** (2×10^{9} CFU/g) and were compared with thirty who received placebo. As for the results, there was a significant reduction in weight (-0.5 ± 0.4 vs. +0.1 ± 1.0 kg, p = 0.004) and BMI (-0.2 ± 0.2 vs. +0.03 ± 0.4 kg/m2, p = 0. 004) compared to placebo, in addition to a reduction in fasting plasma glucose (-2.4 ± 8.4 vs. +2.1 ± 7.0 mg/dL, p = 0.02), serum insulin concentrations (-2.0 ± 5.8 vs. +1.6 ± 5.0 μIU/mL, p = 0. 01), homeostatic model assessment - insulin resistance (-0.5 ± 1.4 vs. +0.3 ± 1.1, p = 0.01), homeostatic model assessment - beta cell function (-7.5 ± 22.3 vs. +6.3 ± 21.7, p = 0. 01), serum triglycerides (-13.3 ± 51.3 vs. +13.6 ± 37.1 mg/dL, p = 0.02) and a significant increase in the quantitative insulin sensitivity check index (QUICKI) (+0.006 ± 0.01 vs. -0.005 ± 0.02, p = 0.01).

Shoaei et al (2015)[14] analyzed the effects of probiotic supplementation on pancreatic β-cells and C Reactive Protein in women with PCOS. Therefore, seventy-two women with PCOS between fifteen and forty years old were divided into two groups according to age and BMI, implying thirty-six women taking a placebo and the other thirty-six consuming probiotic capsules of ***Lactobacillus casei*** 7×10^{9} CFU/g, ***Lactobacillus acidophilus*** 2×10^{9} CFU/g, ***Lactobacillus rhamnosus*** 1.5×10^{9} CFU/g, ***Lactobacillus bulgaricus***, 2×10^{8} CFU/g, ***Bifidobacterium breve*** 2×10^{10} CFU/g**,** ***Bifidobacterium longum*** 7×10^{9} CFU/g, ***Streptococcus thermophiles*** 1.5×10^{9} CFU/g for eight weeks. The results, when compared to placebo, showed a reduction in fasting blood glucose (-4.15 ± 2.87 vs. 2.57 ± 5.66 mg/dL, respectively, P = 0.7) and serum insulin (-0.49 ± 0.67 vs. 0.34 ± 0.82 μIU/mL, respectively, P = 0.09), while there was no significant impact on CRP and pancreatic β-cell function (-0.25 ± 0.18 vs. -0.05 ± 0.18, respectively, P = 0.14).

Darvishi et al (2021)[19] conducted a study that analyzed the supplementation of symbiotics in the improvement of metabolic factors and obesity in women with PCOS, not considering the modulation of apelin 36 levels. Sixty-eight patients were analyzed, in which thirty-four received a placebo and the rest received a capsule containing ***Lactobacillus casei*** 3×10^{9} CFU/g, ***Lactobacillus rhamnosus*** 7×10^{9} CFU/g, ***Lactobacillus bulgaricus*** 5×10^{8} CFU/g, ***Lactobacillus acidophilus*** 3×10^{10} CFU/g, ***Bifidobacterium longum subsp*** 1×10^{9} CFU/g, (strainACS-071-V-Sch8b) 2×10^{10} CFU/g, ***Streptococcus thermophilus*** subsp 3×10^{8} CFU/g inulin-type prebiotics (fructooligosaccharides)[20]. The results showed that the symbiotic supplementation

reduced blood glucose, serum insulin, and HOMA-IR by 1.35, 13.92, and 15.68%, respectively, compared to the placebo group, as well as in the study by Samimi et al[18] and Esmaeilinezhad et al[21]. Significant reductions (2.52% and 1.75%, respectively) were observed in WC (waist circumference) and WHtR (waist-to-height ratio) after the symbiotic intervention compared with baseline values (P = 0.009 and P = 0.02, respectively). Weight and BMI increased in the placebo group (respectively by 0.74%, P = 0.003 and 0.87%, P = 0.003).

Discussion

According to the results found in the study by Samimi et al[17], it can be said that symbiotic supplementation for women with PCOS obtained beneficial effects on serum insulin, homeostasis assessment of insulin resistance (HOMA-IR), quantitative check of insulin sensitivity (QUICK), without interfering with fasting plasma glucose[17]. Furthermore, another analysis indicated that some symbiotics have an immunomodulatory function and directly control hyperglycemia and HOMA-IR[21], with the possible hypothesis, albeit partially, being the improvement of insulin metabolism through modification of the gut microbiota, reduction of endotoxin levels, the elevation of fecal pH, and production of pro-inflammatory cytokines[22]. Furthermore, taking into consideration that PCOS patients are at higher risk of developing metabolic syndrome, the use of symbiotics emerges as a strategy to help reduce its development, as they could increase the secretion of glucagon-like peptides 1 (GLP-1) from enteroendocrine L cells, improving insulin metabolism and reducing glucotoxicity[23].

Similarly, Karimi et al[15] reported that there was also no benefit in HbA1c and two-hour fasting glucose (PGF2h). In this bias, despite previous studies reporting the benefits of probiotic supplementation, capable of modulating the intestinal microbiota [7] as an adjuvant in the treatment of PCOS, in addition to lifestyle changes such as diet and exercise for the control of obesity and inflammation[24], the current research tool does not support this analysis, even reporting improvement in serum levels of apelin 36 and insulin resistance. In general, apelin 36 - an endogenous peptide that binds to the G protein-coupled receptor of the adipokine family - used as a biomarker[25], has its expression increased at the expense of insulin resistance[26].

Studies have established that insulin stimulates the secretion of apelin 36, while apelin 36 inhibits insulin secretion, a modulation that would contribute to the pathogenesis of PCOS[27]. Yet, a previous meta-analysis involving eighty-one studies revealed no significant changes in apelin 36 blood concentrate in patients with PCOS, although no symbiotic intervention was performed, only considering the pathophysiological aspects of this disorder[28]. The absence of significant changes in HOMA-IR, QUICKI, and CRP may be due to factors such as duration of analysis time, methodology, species, strain, amount of the probiotic bacteria used, and age and characteristics of the participants in each study since these are variant factors of each research and may interfere with the result.

It can be said that the results of the study conducted by Ahmadi et al[18], suggest that probiotic supplementation has beneficial effects on weight loss, BMI, blood glucose, triglycerides, and VLDL. Complementing the above study about the glycemic profile, suggests that probiotic intake could improve blood glucose by reducing oxidative stress[29], a phenomenon evident in hyperglycemia[30]. Added to this, one study describes the importance of lactic acid-producing bacterial strains, which would exhibit antioxidant properties[31], as in the case of fermented milk containing ***Lactobacillus acidophilus*** and ***Lactobacillus casei***, which delayed the onset of glucose intolerance, hyperglycemia, and hyperinsulinemia by decreasing oxidative stress in fructose-induced diabetic rats[32]. Similarly, immune modulation responses and decreased systemic inflammation using probiotics could result in better markers of insulin resistance, thus helping glycemic indices[33]. As for triglyceride and VLDL blood concentration, this could be explained due to the change promoted by probiotics in the levels of these compounds through the production of short-chain fatty acids (SCFA), especially propionate, which would inhibit hepatic synthesis of fatty acids[34].

Considering Shoaei et al[14] and previous studies have shown that probiotics perform synergies with the gut microbiota and consequently may influence metabolic and inflammatory conditions, such as insulin resistance, present in PCOS. However, the results found in this study did not corroborate with previous literature, as probiotic supplementation for eight weeks showed no effects on pancreatic CRP and β-cell function. However, after adjusting some variables, only serum insulin concentration showed a significant reduction in the probiotic group compared to the control group. In this follow-up, insulin resistance and compensatory hyperinsulinemia contribute to the androgen excess and luteinizing hormone regulation present in the pathophysiology of PCOS, demonstrating the key role of the microbiota in insulin secretion[35].

Furthermore, the goal of exploring CRP is believed to be due to the fact that the inflammatory markers of PCOS resulting from cytokines are the main risk factor for the development of this pathol-

ogy[36]. The impetus for studying pancreatic β cells, on the other hand, is justified by their possible genetic role in the basis of insulin secretion defects, because worsening insulin resistance amplifies the demand for pancreatic β cells, contributing to ovarian dysfunction, manifested in PCOS by hyperandrogenism and anovulation precisely by compensatory hyperinsulinemia[37]. It should be noted that this study was a pioneer in CRP and pancreatic β-cell analysis and therefore presented as a limitation the lack of hormonal assessment and Oral Glucose Tolerance Test. On the other hand, the discrepancies between this analysis and the similar analysis performed by Darvishi et al. may be explained by the dosage and supplement strains used, as well as the intervention time, purity, and bioavailability[19].

Darvishi et al[19] conducted a study that observed significant reductions in WC (waist circumference) and WHtR (waist-to-height ratio) after the symbiotic intervention compared to baseline values). However, the changes in other anthropometric variables were not significant within the symbiotic group and were not related to changes in serum apelin 36 concentrations, as in the Olszanecka Glinianowic et al study[34] and contrary to what was shown in the Karini et al study[15], in which there was a significant decrease in serum apelin 36 concentrations during supplementation, although a twice higher concentration of supplement was used over a longer period (twelve weeks).

Consequently, a decrease in serum insulin is noted in the group of participants who supplemented with symbiotic, this fact has no concrete justification, but rather characterizes hypotheses, such as the significant differences ($P < 0.05$) between the two groups in average daily energy and carbohydrate intake at the beginning of the study. Another possible hypothesis about the decrease in insulin is that the symbiotic may produce short-chain fatty acids (SCFAs) and indirectly trigger increased insulin sensitivity. In addition, symbiotic also increases mucin production and decreases the amount of gram-negative (inadequate) bacteria in the colon, which promotes improvements in insulin receptor function, lower insulin blood concentration, and increased normal ovarian function[38]. Ultimately, this is the only one performed in PCOS patients who received 500 mg supplement and also does not assess the impacts on the gut microbiota from circulating appending, as well as does not assess the role of this adipokine in the pathogenesis of PCOS.

In this context, limitations such as the short duration of the intervention, changes in the gut microbiota, and short-chain fatty acids, which were not assessed in stool analyses. Finally, we consider the impossibility of generalizing the findings to all women with PCOS, including those of low or normal weight, since the study was conducted only on overweight or obese patients.

Conclusion

In general, the benefits of therapeutic supplementation with symbiotic capsules in women with PCOS were established based on the findings of this review (Table 2). The symbiotic components contain assets capable of modulating intestinal microbiota through several pathophysiological mechanisms, implying the control of exacerbated immune responses present in inflammatory diseases, such as PCOS. Thus, the supplementation provides a reduction in insulin resistance, once they positively interfere in serum insulin concentration, plasma glucose, QUICK and HOMAR-IR indexes, and apelin-36. Thus, it was evidenced the role of specific dietary supplementation as an improvement tool in the clinical status and prognosis in the studied group, also as an adjuvant and synergistic alternative to the conventional treatment of PCOS with metformin. However, further studies must be conducted, due to the limitations and variables found in previous literature, such as divergence in the capsule's composition (species, strain, and the number of bacteria), range of intervention, inclusion criteria, and patient's diet.

Table 2

Summary table of studies included in the present systematic literature review

Dosage	*Results*	*Clarify/hypotheses*	*Reference*
Lactobacillus casei 7×10^9 CFU/g, ***Lactobacillus acidophilus*** 2×10^9 CFU/g, ***Lactobacillus rhamnosus*** 1.5×10^9 CFU/g, ***Lactobacillus bulgaricus*** 2×10^8 CFU/g, ***Bifidobacterium breve*** 2×10^{10} CFU/g, ***Bifidobacterium longum*** 7×10^9 CFU/g, ***Streptococcus thermophiles*** 1.5×10^9 CFU/g for 8 weeks.	• Reduction in fasting blood glucose and serum insulin; • There was no impact on CRP and pancreatic beta-cell function.	• Synergism of probiotics with the gut microbiota; • Genetic role in the defect of insulin secretion in pancreatic beta cells; • Limitation of the study in the hormonal evaluation of the patients; • The intervention of dosage, strains, and bioavailability in the evaluation of PCR.	[17]

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Dosage	*Results*	*Clarify/hypotheses*	*Reference*
Lactobacillus acidophilus 3×10^{10} colony forming units (CFU)/g, ***Lactobacillus casei*** 3×10^{9} CFU/g, ***Lactobacillus bulgaricus*** 5×10^{8} CFU/g, ***Lactobacillus rhamnosus*** 7×10^{9} CFU/g, ***Bifidobacterium longum*** 1×10^{9} CFU/g, ***Bifidobacterium breve*** 2×10^{10} CFU/g ***Streptococcus thermophilus*** 3×10^{8} CFU/g) and probiotic inulin (fructooligosaccharide) for 12 weeks.	• Reduced levels of apelin 36 at the end of the intervention; • There was no change in the HOMA-IR index, QUICKI, and CRP, as well as in HbA1c and two-hour fasting glucose (PGF2h);	• Relationship between apelin 36 and insulin; • Variant factors such as analysis time, methodology, species, strain, quantity, and characteristics of the participants interfered with the research result.	[18]
Lactobacillus acidophilus strain (2×10^{9} CFU/g), *Lactobacillus casei strain* (2×10^{9} CFU/g) and ***Bifidobacterium bifidum*** strain (2×10^{9} CFU/g) added to 800 mg inulin for 12 weeks.	• Significant reduction in serum insulin concentrations, as well as in insulin resistance; • Elevation in the quantitative insulin sensitivity check index (QUICK) and the homeostasis assessment of insulin resistance (HOMA-IR); • No effect on fasting plasma glucose levels.	• Immunomodulatory function of probiotics controlling hyperglycemia and insulin resistance; • Secretion of peptides capable of improving insulin metabolism and reducing glucotoxicity.	[14]
Lactobacillus acidophilus (2×10^{9} CFU/g), ***Lactobacillus casei*** (2×10^{9} CFU/g), and ***Bifidobacterium bifidum*** (2×10^{9} CFU/g) for 12 weeks.	• Reduced fasting plasma glucose, serum insulin concentrations, homeostatic beta-cell function-evaluation model, and serum triglycerides; • Increase in the insulin sensitivity check index (QUICK).	• Inhibition of VLDL- and triglyceride-carrying fatty acids; • Reduction of oxidative stress through antioxidative properties.	[15]
Lactobacillus casei 3 ×109 colony forming units (CFU)/g, genus ***Lactobacillus Lactobacillus rhamnosus*** 7×10^{9} CFU/g, ***Lactobacillus bulgaricus*** 5×10^{8} CFU/g, genus ***Lactobacillus acidophilus*** 3×10^{10} CFU/g, ***Bifidobacterium longum*** subsp 1×10^{9} CFU/g, (strainACS-071-V-Sch8b) 2×10^{10} CFU/g ***Streptococcus thermophilus*** subsp3 $\times 10^{8}$ CFU/g inulin-type prebiotics (fructooligosaccharides FOS) 500mg, for 8 weeks.	• Reduction of blood glucose, serum insulin, HOMA-IR, as well as WC and WHtR • There was no change in the levels of apelin 36; • Increased weight and BMI in the group that did not receive intervention.	• The limitation of the study is not evaluating short-chain fatty acids; • Significant differences between the two groups in average daily energy and carbohydrate intake; • Increased insulin sensitivity due to fatty acid production; • Improvements in insulin receptor function due to increased mucin production.	[19]

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Conflict of interest: E.T.V., J.K., M. G. P, and C.R.O. declare no conflict of interest.

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