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A SYSTEMATIC REVIEW ON CURRENT TREATMENT OPTIONS FOR INSULIN RESISTANCE IN POLYCYSTIC OVARY SYNDROME

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ABSTRACT: Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine disorder affecting women of reproductive age. It is characterized by symptoms such as elevated androgen levels, the presence of multiple cysts on the ovaries, irregular or absent ovulation and various metabolic disturbances. Women with PCOS commonly experience metabolic dysfunction, obesity and infertility. They also face a higher risk of pregnancy complications and long-term cardiovascular disease. About 75% of individuals with PCOS have Insulin Resistance (IR). IR can trigger symptoms of PCOS, but hyperandrogenemia related to PCOS can also worsen IR. This review aims to summarize the current treatment options for managing IR in PCOS and to prevent the long-term complications associated with it. Current treatment strategies include lifestyle modifications, which remain foundational for improving metabolic health, alongside pharmacological interventions such as *Metformin*, Thiazolidinediones, GLP-1 Receptor Agonists (GLP-1 RA) and SGLT-2 (Sodium Glucose Co-transport) inhibitors. These established therapies offer significant benefits in managing IR and associated symptoms. Additionally, *Inositol* has gained recognition for its role in supporting metabolic and reproductive outcomes. Emerging treatments also show promise, including *Alpha-Lipoic Acid* (*ALA*), Probiotics, Green Tea Extracts (GTE), *L-Carnitine*, *Astaxanthin* (*ASX*), *Resveratrol*, *N-Acetylcysteine (NAC)*, *L-Arginine*, *Berberine*, *Vitamin D*, Omega-3 fatty acid, *Chromium* and *Magnesium*. As our understanding of PCOS and IR continues to advance, integrating both current and emerging therapies will be key to improving patient outcomes and quality of life.

INTRODUCTION: Polycystic Ovary Syndrome (PCOS) is a reproductive age disorder affecting women, that is marked by high level of androgen, the existence of multiple cysts on the ovaries, irregular or absent ovulation and various metabolic disturbances [1]. The global prevalence of PCOS is approximately 9.2%, with the highest rate observed in Africa, where it reaches 16.4% [2].

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Obesity and being overweight are commonly linked with PCOS, with observational studies indicating that 33% to 88% of women with PCOS are affected by these conditions [3, 4]. Diagnosis is advised using the 2003 Rotterdam criteria, which require meeting at least any two of this presentation: hyperandrogenism, Polycystic Ovary Morphology (PCOM) and irregular menstrual cycle [5].

PCOS is usually accompanied by obesity, metabolic dysfunction and infertility. They are also at risk of developing complications during pregnancy and early cardiovascular disease [6-11]. It greatly affects quality of life and causes Non-Alcoholic Fatty Liver Disease (NAFLD), metabolic

diseases and Type 2 Diabetes Mellitus (T2DM) [12-14]. Central obesity is particularly important due to its association with hyperandrogenism and Insulin Resistance (IR) [15].

The patient frequently has IR and diminished amount of sex hormone-binding globulin (SHBG). SHBG is normally formed by liver, which binds to sex hormones like testosterone and estradiol. When SHBG levels are low, there are higher amounts of free testosterone, leading to hyperandrogenemia. Low SHBG levels are seen as a marker of metabolic abnormalities and are linked to IR because high insulin levels reduce SHBG production in the liver [16]. About 75% of individuals with PCOS have IR [17]. IR can trigger symptoms of PCOS, but hyperandrogenemia related to PCOS can also worsen IR. Women with PCOS are frequently exposed to traditional cardiovascular disease (CVD) risk factors over the long term, as they often exhibit obesity, IR, impaired glucose metabolism, dyslipidemia and elevated Blood Pressure (BP) from a young age or even during adolescence [18].

This review aims to summarize the current treatment options for managing IR in PCOS and to prevent the long-term complications associated with it.

MATERIAL AND METHODS:

Study Design: This systematic review aimed to evaluate the current treatment options for IR in PCOS. The review was written as per the PRISMA guidelines, to ensure proper methodology and comprehensiveness. All included studies were assessed based on their design, sample size, treatment interventions, outcome measures and quality.

Inclusion and Exclusion Criteria: Studies investigating treatment strategies for IR in PCOS, including pharmacological and non-pharmacological therapies. Studies published in English, Studies that assessed clinical and/or biochemical outcomes of IR in PCOS, such as insulin sensitivity indices, fasting glucose, HbA1c, and lipid profiles were included.

Those studies focusing on PCOS without assessing IR, non-original research articles, such as letters and editorials, studies that did not report specific data on IR outcomes, studies with incomplete data or insufficient information on treatments were excluded.

Search Strategy: A thorough probe of the literature was performed using the electronic databases like PubMed, Cochrane Library, EMBASE and google scholar. The search for the current article was done for studies published from the period of January 2000 and January 2025. The search strategy included the following key terms and their combinations:"Polycystic Ovary Syndrome" or "PCOS", "Insulin resistance" or "IR", "Treatment options" or "Management" or "Therapies", "Pharmacological treatment" or "non-pharmacological treatment", "Metformin", "Insulin sensitizers", "Vitamin D", "Omega-3", "Chromium", "Curcumin".

Relevant articles were screened using the abstracts and the titles. Also, the entire article text was reviewed for potentially eligible studies to ensure compliance with inclusion criteria and exclusion criteria.

Extraction of Data: With the help of standardized form for data extraction, data so collected were extracted independently.

Synthesis and Analysis of Data: The collected data from all the studies, were qualitatively synthesized. The effectiveness of each treatment modality was assessed in terms of improvements in insulin sensitivity, metabolic outcomes and hormonal regulation.

RESULTS & DISCUSSION:

Mechanism of Insulin Resistance (IR) in PCOS: Recent studies have suggested that PCOS is influenced by multiple determinants like environmental changes, epigenetic changes, oxidative stress, genetics, mitochondrial derangement and chronic low-grade inflammation, all of which can disrupt normal ovarian function [19-26]. IR and compensatory hyperinsulinemia are regarded as key factors in the pathophysiology of PCOS. They contribute to the advancement of hyperandrogenemia and subsequent reproductive complications through multiple processes [27]. IR is the most common type of PCOS phenotype [28]. PCOS is linked to gene mutations especially in the genes that control steroid production, signalling of

insulin and development of follicles in ovary. It was also found to affect multiple proteins like activators of LH/HCG receptor, transcription factors, insulin receptors, and cell traffic proteins [29, 30]. Further it is complicated by high serine phosphorylation and low tyrosine phosphorylation of insulin receptors, that affect the action of insulin. This results in defective transduction of insulin after binding, thereby contributing to defective action of insulin [31].

IR is characterized by reduced sensitivity of target organs such as the liver, skeletal muscle, and adipose tissue to insulin, leading to decreased effectiveness of insulin in facilitating glucose uptake and utilization. To compensate, the body increases insulin production, resulting in hyperinsulinemia to stabilize blood sugar levels. Persistent hyperinsulinemia is a hallmark feature often observed before the onset of PCOS. In 1980, Burghen first suggested that IR act as a crucial component in the formation of PCOS. Later studies confirmed that it is a fundamental initiating factor for the development of PCOS [32]. Moreover, factors such as excessive androgens, lipid accumulation, inflammatory cytokines and other systemic elements also contribute to IR in peripheral tissues [33].

Because of IR, patients with PCOS are at greater risk of developing negative outcome during pregnancy as well as chronic conditions like T2DM, CVD and metabolic syndrome. These related issues add to the social burden for women of childbearing age [34-38].

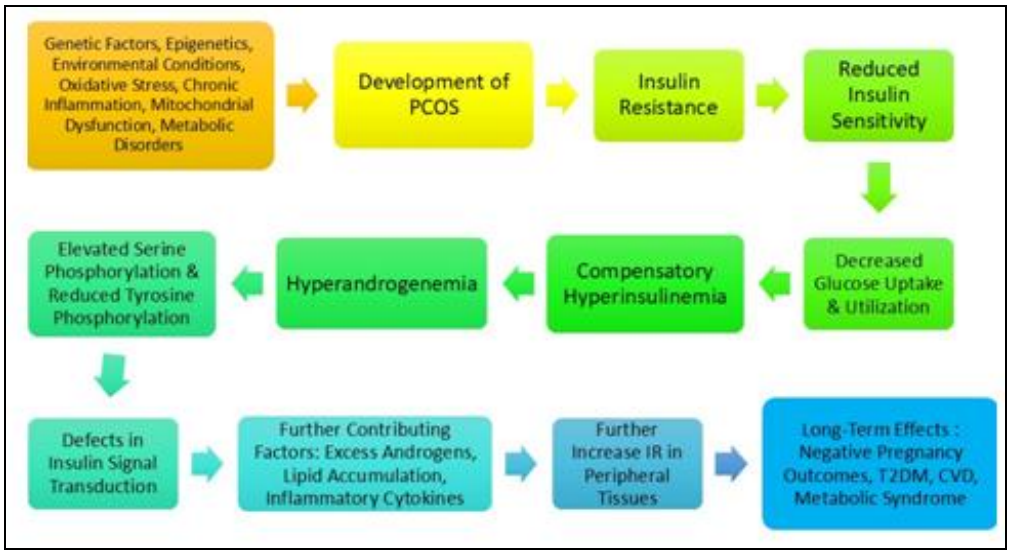

FIG. 1: MECHANISM OF INSULIN RESISTANCE IN PCOS

Treatment Options for Insulin Resistance in PCOS: The management of PCOS should consider not just the patient needs but also any associated comorbidities. IR and hyperandrogenism are key characteristics of the syndrome in PCOS individuals [39]. IR is a primary focus of treatment along with Combined Oral Contraceptives (COC) [40].

Current Treatment Options:

Lifestyle Change: The initial approach to managing IR involves making lifestyle changes, which are fundamental for improving the associated metabolic disorders and endocrine changes in women with PCOS [41]. This is possible by a change in diet and by adopting an exercise regimen [42]. Exercise enhances insulin sensitivity through its effects on increasing the transport of glucose and thereby enhancing metabolism. This is said to be the prime important aspect of PCOS treatment. Both moderate and high-intensity aerobic exercise are effective in treating IR. The recommended exercise regimen consists of exercising at least 30 minutes per day for around 3 to 5 times a week. Even a single exercise session can boost insulin sensitivity for up to 2-72 hours afterward. Regular exercise not only improves insulin sensitivity and glycemic control but also helps reduce abdominal fat, making it a valuable strategy for managing IR in women with PCOS [43]. Research has demonstrated that the Mediterranean

diet which focuses on including large quantities of mixed vegetables, seafood, nuts, fruits, and whole grains. It also includes a diet rich in low-carbohydrate that is combined with vegetable oils. This can positively impact menstrual cycles in PCOS patients, especially who are overweight [44]. Sleep deprivation is linked to a higher risk developing overweight, IR and T2DM in PCOS. Consequently, managing sleep must be included as a component of lifestyle modifications for these women [45].

***Metformin*:** *Metformin* is the one of the commonly used medications because of its proven efficiency in PCOS and safety profile. Its positive effects are becoming more apparent, particularly when used alongside lifestyle changes. *Metformin* helps address the underlying mechanisms of PCOS, restores function of ovaries and enhances the metabolic status, notably improving the sensitivity of insulin. In contrast to COCs, it positively affects lipid levels [46]. Recent research on *Metformin* shows that it decreases the ongoing inflammation in PCOS both directly and indirectly, because of its anti-inflammatory properties. Its effect appears to control the balance of T-cell, as observed in mice [47]. During *Metformin* treatment, serum IL-6 levels decreased in conjunction with improvements in IR [48].

The typical doses for PCOS studied and prescribed are 500 mg given for three times daily or 850 mg given twice a day. It is usually started at a lower dose to prevent any gastrointestinal discomfort and then its dose is slowly increased to achieve the target dose. Previous study on 360 young patients with PCOS and normal kidney function, showed no instances of developing lactic acidosis [49].

Thiazolidinediones: Thiazolidinediones (TZD) are known as an effective sensitizer of insulin. TZDs can serve as an alternative treatment for metabolic and reproductive issues related to PCOS who either doesn't tolerate *Metformin* or shows poor response to it [50-52]. The TZDs such as *Rosiglitazone* and *Rosiglitazone* were linked to notable increases in the BMI when compared in studies to placebo or *Metformin*. *Pioglitazone* notably lowered fasting levels of insulin and triglycerides when evaluated against a placebo. *Rosiglitazone,* was found to decrease LH levels when evaluated against *Metformin* [53]. Moreover, they help regulate menstrual cycle irregularities, stimulate the ovulation process and lower the level of androgen PCOS [54, 55]. But, clinically its use is limited because of several known side effects like peripheral edema, weight gain and heart failure [56].

Glucagon like Peptide-1 Receptor Agonist (GLP-1 RA): GLP-1, a type of in cretin hormone, can promote release of insulin as a response to levels of glucose. GLP-1 receptor agonist mimics this effect, as they also attach to the GLP-1 receptor and stimulate the secretion of insulin from islets of pancreas in a way of glucose-dependent manner. Besides this primary action, GLP-1 analogues help slow down gastric transit and reduce secretion of the hormone glucagon from alpha cells of pancreas [57].

In a randomized trial, PCOS patients with obesity, who was treated with the drug *Metformin* were given either *Liraglutide* at a dose of 1.2mg daily or *Metformin* at a dose of 1000mg twice daily. The results showed that *Liraglutide* led to greater reductions in BMI, with a decrease of 1.1 ± 1.26 kg/m² compared to *Metformin*. Additionally, *Liraglutide* was found to decrease the area of visceral adipose tissue [58].

In a study, on 72 PCOS patients with overweight were given with either 1.8 mg per day of *Liraglutide* or a placebo over a period of 26 weeks. The results indicated that the drug *Liraglutide* significantly decreased body weight, liver fat, visceral adipose tissueand free testosterone levels [59].

Liraglutide treatment, which was associated with weight loss, significantly reduced levels of Procollagen type 3 amino-terminal Peptide (PIIINP). This peptide is said to be an indicator of cirrhosis of liver, especially in obese patients with PCOS. This finding adds a new dimension to the evaluation of *Liraglutide*'s use in women with PCOS, obesity and NAFLD [60]. GLP-1 RAs have shown a great reduction in fasting blood glucose, IR, total cholesterol and triglycerides level. In a clinical trial involving 150 patients with PCOS who had impaired glucose and fasting tolerance, it was found that 32% had remission of prediabetes with *Metformin*, 56 % had remission with *Exenatide*

alone and around 64% had remission by using combined treatment [61]. Combining GLP-1 RA with *Metformin* appears to be more effective than using either medication alone [62, 63].

***Inositol*:** As insulin sensitizers, *Inositol* was found to enhance both metabolic and endocrine parameters of PCOS. Previous studies have proven its benefits by improving hyperandrogenic parameter in PCOS. The two most common forms of inositol in humans are *D-chiro-inositol* (*DCI*) and *Myo-inositol* (*MYO*), which are primarily obtained from dietary sources. *MYO* was converted into its another form *DCI* in the presence of an enzyme called epimerase, which is stimulated by insulin. This conversion helps regulate the *DCI/MYO* ratio across different organs and tissues, that are involved in mediated various processes in body like remodelling of cytoskeleton, developmental mechanism, permeability of ion channel, signal transduction in endocrine process and stress mechanism.

Research has confirmed that *MYO* and *DCI* are known as insulin sensitizers mediating oxidative balance and enhancing metabolic role [64]. *MYO* is involved in enhancing the FSH signalling by acting as a second messenger in ovaries. Thereby, it controls the process of ovulation and menstrual cycle. As a result, it improves the production and quality of oocyte. Also, it was found that taking *DCI* supplementation without *MYO* can lead to increased insulin dependent androgen production, causing poor fertility outcome in PCOS.

Combining *DCI* and *MYO* in a ratio of 1:40 closely resembles the normal ratio found in plasma of a women. It was proven to benefit IR in PCOS, as it enhances the metabolic parameter and function of ovary [65]. Additionally, combining this with COC or *Metformin* exerts a synergistic effect and thereby decrease the potential side effects [66].

Sodium-Glucose Co-transporter 2 Inhibitors: Sodium-Glucose co-transporter 2 inhibitors (SGLT-2 Inhibitors) act by attaching to SGLT-2 receptors which are found in the proximal convoluted tubule of the kidney, thereby inhibiting the reabsorption of glucose and sodium.

This results in lower blood glucose levels, increased glucose in the urine (glucosuria) and enhanced sodium excretion (natriuresis), which helps reduce BP. They promote glucose excretion at a rate of 60-80 grams per day, leading to an average weight loss of around 1.7 kg in a person. The effectiveness of SGLT-2 inhibitors is independent of IR, beta-cell function and insulin secretion. Additionally, it further lower levels of blood glucose by enhancing sensitivity of insulin, boosting uptake of glucose in muscles, reducing gluconeogenesis process in the liver and enhancing the initial stage of insulin release from the beta-cells of pancreas [67, 68]. Research indicates that SGLT-2 inhibitors may help preserve function of beta cell indirectly by decreasing insulin secretion while enhancing glucagon release. This process contributes to increased lipolysis and reduced fat in the liver and visceral adipose tissue [69].

TABLE 1: CURRENT TREATMENT OPTIONS FOR INSULIN RESISTANCE IN PCOS

Drug Category	Drug	Dose	Mechanism of action	Side effects	How It Reduces Insulin Resistance in PCOS?	Ref.
Biguanide	*Metformin*	500 mg 3x/day or 850 mg 2x/day	Increases insulin sensitivity, restores ovarian function, improves metabolic profile, anti-inflammatory effect	Gastrointestinal discomfort, lactic acidosis (rare)	Improves metabolic parameters and insulin sensitivity, reduces inflammation, enhances ovarian function.	[46-49]
Thiazolidinediones (TZD)	*Pioglitazone* *Rosiglitazone*	15-45 mg/day 4-8 mg/day	PPAR-γ agonist, insulin sensitizer	Weight gain, peripheral edema, heart failure	Regulates menstrual cycles, stimulates ovulation, lowers androgens, increases insulin sensitivity.	[50-56]
GLP-1 Receptor Agonists	*Liraglutide* *Exenatide*	1.2-1.8 mg/day 5-10 mcg twice a	Mimics GLP-1, increases insulin release, reduces gastric emptying,	Nausea, diarrhea, Vomiting, headache	Reduces BMI, visceral adipose tissue, free testosterone, improves insulin sensitivity and	[57-63]

		day	decreases glucagon production		metabolic outcomes.	
Inositol	*Myo-inositol D-chiro-inositol*	2-4 g/day 600 mg-2 g/day	Acts as an insulin sensitizer, regulates DCI/MYO ratio	Minimal side effects, may cause mild gastrointestinal discomfort	Restores menstrual cycles, improves ovarian function, enhances metabolic profiles by improving insulin sensitivity.	[64-66]
SGLT-2 Inhibitors	*Empagliflozin* *Canagliflozin*	10mg/day 100-300 mg/day	Inhibits glucose reabsorption in kidneys, promotes glucosuria, reduces blood glucose levels	Urinary tract infections, dehydration, hypotension	Decrease level of glucose, enhances insulin sensitivity, accelerates weight loss, lowers visceral fat and liver fat.	[67-69]

Emerging Treatment Options:

***Alpha-Lipoic Acid*:** *Alpha-lipoic acid* (*ALA*) is a known biological compound having strong antioxidant properties, found in various vegetables like spinach, broccoli and potatoes, as well as in red and organ meats such as the liver and heart.

Genazzani *et al.* administered 400 mg/day of ALA to obese women with PCOS for 12 weeks and observed significant improvements in several parameters, including insulin levels, glucose level, BMI, insulin response to OGTT, the HOMA index and maximal insulin response [70]. It reduces IR and oxidative damage in PCOS.

Probiotics: Numerous studies have found the association between PCOS and alterations in gut microbiota. Studies have shown a notable difference in gut microbiome composition between patients with PCOS and healthy individuals [71]. For instance, Singh *et al.* found that diets high in proteins of animal origin were linked to increased levels of *Alistipes, Bacteroides* and *Bilophila,* along with decreased amount of *Bifidobacterium adolescentis,* a microbiota that was associated with a higher risk of developing cardiovascular disease [72]. PCOS is a state of inflammation contributing to dysfunction of pancreatic beta-cell, IR and process of atherogenesis.

It was found that a 12-week regimen combining a mixture of probiotic consisting of *Lactobacillus reuteri, Lactobacillus acidophilus, Bifidobacterium bifidum* and *Lactobacillus fermentum* with a daily supplementation selenium in a dose of 200 mg leads to improvements in serum total testosterone levels, hs-CRP, hirsutism, total antioxidant capacity, mental health and malondialdehyde levels [73].

Green Tea Extracts: Studies on Green Tea Extracts (GTE) have shown that IR can be improved through increased representation of glucose transporter 4 (GLUT-4) in adipocytes [74]. GTE enhances both basal and insulin mediated uptake of glucose in adipocytes, thereby decreasing glucose absorption in the small intestine [75]. It was found to decrease insulin resistance in obese and overweight women with PCOS following GTE consumption. Tehrani *et al.* demonstrated that a daily supplementation in a dose of 500 mg for 3 months reduced fasting insulin, blood glucose and free testosterone levels in overweight PCOS patients [76]. Similarly, Allahdadian *et al.* found that GTE when given for 3 months significantly reduced serum insulin and FBS levels.

It is important to recognize that while green tea has beneficial effects, over consumption may lead to adverse effect. It was found that the effect of green tea catechins might differ among individuals. For example, *Epigallocatechin Gallate* (*EGCG*) may act as cytotoxic and frequent intake of green tea leads to acute cytotoxicity in liver cells. Additionally, another research has shown that *EGCG* can act as a pro-oxidant in pancreatic beta cell. Consequently, patients should be cautioned against excessive and unregulated use of green tea, particularly its extracts [77, 78].

***L-Carnitine*:** *Carnitines* are quaternary amines that can be either ingested through intake or produced in the body. It functions as vitamin like compounds and exist in two forms which are *L-carnitine*, the important active form needed for cellular energy production and *D-carnitine,* which is inactive and might be toxic. Previous studies have found that *L-carnitine* can lower levels of insulin and enhance

serum adiponectin levels. Treatment with *L-carnitine* was associated with a reduction in HOMA-IR, as well as notable improvements in testosterone, FSH, and LH levels [79]. However, a clinical trial of 12-week found that *L-carnitine* had no significant impact onlipid profile and SHBG [80]. Additionally, targeting the kisspeptin and neurokinin B (NKB) pathways may become a promising novel therapy for tackling hyperandrogenic symptoms of PCOS [81].

***Astaxanthin*:** *Astaxanthin* (*ASX*) is a known carotenoid that is found naturally numerous seafood and microorganisms. Previous studies have found that *ASX* when consumed for 8 weeks has resulted in decrease of HOMA-IR, Fasting blood glucose, FI, LDL, MDA, and TC/HDL-C. Conversely, it has prominently elevated HDL-C, TAC and QUICKI [82]. On the other hand, *ASX* lowered serum levels of pro-inflammatory markers, including IL-18, IL-6, TNF-α and CRP, in patients with PCOS [83]. Multiple studies have explored various therapeutic approaches that show promise in alleviating symptoms associated with PCOS, such as infertility, menstrual cycle irregularity, BMI, IR and hirsutism [84, 85].

***Resveratrol*:** *Resveratrol* is a natural polyphenol found in various fruits, including grape skins, peanuts and red wine, as well as in several plant-based medicinal sources [86, 87]. In a study, the effect of *Resveratrol* in a dose of 800 mg/day for around 40 days on the levels of serum inflammatory markers in PCOS was determined [88]. The treatment led to reductions in serum levels of IL-6, IL-1beta, TNF-alpha, IL-1beta, IL-18, CRP and NFkB. Another study by Ghowsi *et al.* investigated the effects of *Resveratrol* when injected intraperitoneally at a dose of 10 mg/kg in PCOS-induced Wistar rats, which exhibited enhanced peroxidation of lipid and IR [89]. *Resveratrol* improved these conditions and the levels of two inflammatory markers in adipocytes were found to be significantly reduced in the PCOS rats treated with *Resveratrol* compared to untreated ones. These markers were like those in control rats, indicating that *Resveratrol* treatment potentially normalized inflammatory marker levels and reduced inflammation associated with PCOS. A study indicated that *Resveratrol* supplementation could be beneficial in managing PCOS-related symptoms by decreasing IR, improving dyslipidemia, enhancing morphology of ovaries and anthropometric measurements, controlling hormones of reproductive system, reducing inflammation and related oxidative stress through various biological pathways. This evidence suggests that *Resveratrol* may help alleviate PCOS complications [90].

***N-Acetyl Cysteine* & *L-Arginine*:** *N-acetyl-L-cysteine* (*NAC*) is widely prescribed as a mucolytic drug and to treat toxicity of acetaminophen. At greater doses, it boosts the reduced glutathione (GSH) at cellular levels and neutralizes formed free radicals such as superoxide and hydrogen peroxide, functioning as an essential antioxidant. Arginine serves as the substrate for Nitric Oxide Synthase (NOS) during the synthesis of Nitric Oxide (NO). Masha *et al.* showed that administering *N-Acetyl Cysteine* at a dose of 1200 mg and *L-Arginine* at a dose of 1600 mg for a period of six months has resulted in an increased frequency of menstrual cycles and improved insulin sensitivity, as evidenced by a reduced HOMA index in PCOS. These findings further prove the hypothesis that *L-Arginine* and *NAC* enhance ovarian function by increasing nitric oxide (NO) availability [91].

***Berberine*:** *Berberine* was known as an isoquinoline alkaloid found in various herbal products, has a history of been used in Chinese and Ayurvedic medicine. It is recognized for its strong antimicrobial properties, effective against fungi, bacteria, protozoa, helminths, virusesand chlamydia. In women with PCOS, berberine can influence various metabolic factors by reducing IR and increasing the active phosphorylation of insulin receptors and alsoinsulin receptor substrate-1 (IRS1) in adipocytes [92].

***Chromium*:** *Chromium* plays a role in fat and carbohydrate metabolism and has been found to improve IR in PCOS by enhancing insulin receptor expression and activating proteins like Akt and GLUT4, which are involved in insulin signaling. It also exerts anti-inflammatory effects, improving insulin sensitivity. Studies have shown that chromium can help with weight management and reduce androgen levels in PCOS patients. It is been commonly administered in form of *chromium polynicotinate* and *chromium picolinate*.

While generally considered safe, high doses may cause gastrointestinal side effects. Hence, it should be used as a complementary therapy [93-96].

Omega-3 Fatty Acids: Omega-3 fatty acids used as supplementation are *DHA* and *EPA*, have shown favorable effects in treating IR in PCOS by exhibiting anti-inflammatory properties, enhancing insulin receptor signaling and improving lipid profiles. Studies have indicated that they can enhance insulin sensitivity and reduce androgen levels. They are commonly administered in the form of Fish oil supplements. At high doses, they may result in gastrointestinal side effects [97-101].

Vitamin D: Vitamin D is a crucial vitamin needed for immune health and bone density and has proven benefits in improving insulin sensitivity in patients with PCOS. It works by helping maintain calcium homeostasis and exhibiting anti-inflammatory effects. Studies have observed that administering vitamin D has resulted in decreased androgen levels and thereby attenuates IR in PCOS. The most used vitamin D forms are Vitamin D2 (*ergocalciferol*) and Vitamin D3 (*cholecalciferol*). While generally safe, high doses may lead to hypercalcemia and interactions with medications like calcium channel blockers and thiazide diuretics [102-107].

***Curcumin*:** *Curcumin*, derived from turmeric, is known for its anti-inflammatory and antioxidant properties. In PCOS, it has been found to decrease androgen levels and improve insulin sensitivity. Common forms of curcumin used in supplements include *curcuminoids* and *curcumin phytosome*, the latter improving bioavailability. They might cause mild gastrointestinal side effects in some patients [108-113].

***Magnesium*:** *Magnesium* is involved in insulin signalling and glucose metabolism. It helps improve pancreatic beta-cell function, modulate inflammation and regulate insulin tyrosine kinase activity. It was found that administering *Magnesium* as supplements might enhance insulin sensitivity in PCOS. The most used *Magnesium* forms are *Magnesium citrate* and *Magnesium oxide*, with the latter being better absorbed. At higher doses, it can lead to diarrhoea [114-118].

TABLE 2: EMERGING TREATMENT OPTIONS FOR INSULIN RESISTANCE IN PCOS

Drug	Mechanism of Action	Dose & Route of Administration	Study Outcome	How It Can Be Used to Reduce IR in PCOS?	Side Effects	Ref.
Alpha-Lipoic Acid (ALA)	Antioxidant; reduces oxidative stress and insulin resistance.	400 mg/day, oral, for 12 weeks	Significant improvements in insulin levels, glucose levels,BMI, insulin response to OGTT, HOMA index and maximal insulin response.	Reduces oxidative damage and insulin resistance in PCOS.	Generally well tolerated, but high doses may cause mild side effects like skin rash, headache.	[70]
Green Tea Extract (GTE)	Increases glucose transporter 4 (GLUT-4) expression and reduces glucose absorption.	500 mg/day, oral, for 3 months	Significant reduction in insulin resistance, FBS, insulin, and free testosterone in overweight women with PCOS.	Enhances insulin sensitivity, reduces blood sugar and testosterone levels in PCOS.	Excessive intake can cause liver toxicity, GI distress, and cytotoxicity in high doses.	[74-78]
Probiotic Mixture (*Bifidobacterium bifidum, Lactobacillus acidophilus, Lactobacillus fermentum, Lactobacillus reuteri*)	Improves gut microbiome and reduces inflammation, thus helping with insulin resistance.	12-week regimen, oral with selenium 200 mg/day	Improvements in hirsutism, serum testosterone levels, total antioxidant capacity, hs-CRP, malondialdehyde levels.	Modulates gut microbiota, reduces inflammation, and improves insulin sensitivity in PCOS.	Mild gastrointestinal disturbances like bloating, gas.	[71-73]
L-Carnitine	Increases	Oral	Reduced insulin	Improves insulin	Generally safe,	[79-

	cellular energy production and reduces insulin levels.	administration	levels and improvements in testosterone, FSH, and LH levels. No impact on SHBG or lipid profile.	sensitivity, reduces testosterone and enhances ovarian function in PCOS.	but may cause mild gastrointestinal issues such as nausea.	81]
Astaxanthin (ASX)	Reduces oxidative stress, inflammation, and insulin resistance; improves lipid profiles.	Oral administration	Reduced fasting blood sugar, LDL,HOMA-IR and inflammation markers. Increased TAC and HDL-C.	Reduces oxidative stress, improves insulin resistance, and reduces inflammation in PCOS.	Mild gastrointestinal discomfort.	[82-85]
Resveratrol	Reduces inflammatory markers, oxidative stress, and insulin resistance.	800 mg/day, oral, for 40 days	Reduced inflammatory markers (IL-6, TNF-alpha, IL-1beta) and insulin resistance.	Improves insulin resistance, reduces inflammation, and improves lipid metabolism in PCOS.	GI upset, headache, allergic reactions in some individuals.	[86-90]
N-Acetyl Cysteine (NAC) & L-Arginine	NAC boosts glutathione levels; L-Arginine increases nitric oxide production, improving insulin sensitivity.	NAC -1200 mg, L-Arginine - 1600 mg, oral, for a period of 6 months	Increased menstrual cycles and improved insulin sensitivity (decreased HOMA index).	Enhances ovarian function and insulin sensitivity by increasing nitric oxide availability.	Possible mild gastrointestinal disturbances, headache.	[91]
Berberine	Reduces insulin resistance, enhances insulin receptor phosphorylation.	Oral administration	Improved insulin sensitivity and reduced IR	Enhances insulin receptor function, reduces insulin resistance in PCOS.	Gastrointestinal issues like diarrhea, constipation, or bloating.	[92]
Chromium	Enhances insulin receptor expression, activates proteins like Akt and GLUT4, exerts anti-inflammatory effects.	200–1000 mcg/day, oral. Typically in chromium picolinate or polynicotinate form.	Improved insulin sensitivity, weight management, and reduced androgen levels in PCOS patients.	Increases glucose uptake and insulin sensitivity through insulin receptor activation and anti-inflammatory effects.	GI issues (nausea, vomiting, diarrhea), possible interactions with medications like beta-blockers and blood thinners.	[93-96]
Omega-3 Fatty Acid	Exhibits anti-inflammatory effects, enhances insulin receptor signaling, improves lipid profiles.	1000–3000 mg/day (EPA/DHA), oral. Commonly in fish oil supplements.	Improved insulin sensitivity and reduced androgen levels in PCOS patients.	Enhances insulin receptor signaling and improves lipid profiles, reducing insulin resistance and metabolic complications.	GI discomfort (nausea, vomiting, diarrhea), possible interactions with blood thinners and anti-inflammatory meds.	[97-101]
Vitamin D	Maintains calcium homeostasis, exerts anti-inflammatory	1000–4000 IU/day, oral. Typically as Vitamin D3 (cholecalciferol)	Reduced androgen levels, improved insulin sensitivity, and reduced IR in PCOS.	Improves insulin sensitivity and metabolic complications, reducing insulin	Hypercalcemia, kidney stones, interactions with calcium channel blockers and	[102-107]

	effects, increases insulin receptor expression, improves insulin sensitivity.	.		resistance and inflammation.	diuretics.	
Curcumin	Anti-inflammatory and antioxidant properties, improves insulin sensitivity and reduces androgen levels.	500–1000 mg/day (curcuminoids), oral. Can also be used in curcumin phytosome for enhanced bioavailability.	Reduced insulin resistance, improved insulin sensitivity, and decreased androgen levels in PCOS.	Reduces oxidative stress, improvingsensitivity of Insulin and metabolic outcomes in PCOS.	GI disturbances (nausea, vomiting, diarrhea), interactions with blood thinners and diabetes drugs	[103-113]
Magnesium	Modulates insulin signaling, improves beta cell function, regulates tyrosine kinase activity, modulates inflammatory response.	300–600 mg/day, oral. Typically magnesium citrate or oxide.	Improved insulin sensitivity and beta cell function in PCOS.	Improves insulin sensitivity by modulating insulin signaling and reducing inflammation.	GI issues (nausea, vomiting, diarrhea), interactions with blood thinners and antibiotics.	[114-118]

Future Direction to Treat IR in PCOS: The future strategies for treatment option of IR in PCOS must focus on personalized medicine to be tailored for individual needs. A combination therapy in the form of combination pill must be used widely to improve compliance. Stem cell therapy can play a role in cure of this condition in future. Use of AI in integrating nutrition and exercise with routine treatment can play a significant role. Continued research into the genetic, metabolic, hormonal, and inflammatory pathways will offer exciting opportunities for improving treatment outcomes and addressing the root causes of insulin resistance in PCOS.

CONCLUSION: In conclusion, the management of IR in PCOS has evolved with a diverse array of treatment options, reflecting the complexity of this condition. The current treatment strategies include lifestyle modifications, which remain foundational for improving metabolic health, alongside pharmacological interventions such as *Metformin*, TZD, GLP-1 RA and SGLT2 inhibitors. These established therapies offer significant benefits in managing insulin resistance and associated symptoms. Additionally, *Inositol* has gained recognition for its role in supporting metabolic and reproductive outcomes.

Emerging treatments also show promise, including *ALA*, *Probiotics*, GTE, *L-Carnitine*, *ASX*, *Resveratrol*, *NAC*, *L-Arginine*, *Berberine*, *Chromium*, Vitamin D, Omege-3 Fatty Acid, *Curcumin* and *Magnesium*. While these options are still under investigation, preliminary findings suggest they may provide additional benefits by targeting IR and enhancing overall metabolic function.

The combination of well-established and emerging therapies offers a comprehensive approach to managing insulin resistance in PCOS. Future research will be crucial in combining these emerging treatments and optimizing personalized treatment plans. As our understanding of PCOS and IR continues to advance, integrating both current and novel therapies will be crucial in enhancing quality of life.

Author Contribution: In this review paper, the author contribution is crucial in compiling an extensive overview of current research and applications related to treatment options for insulin resistance in T2DM. The author has carefully examined and analysed a wide range of scientific literature, offering a thorough evaluation of both current and investigational treatment options

available. By systematically assessing recent developments and ongoing discussions in the field, the authors have created a detailed narrative that underscores both well-established knowledge and emerging trends. Additionally, the author has reviewed and approved the final manuscript.

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