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Review

Effects of Resveratrol on Metabolic, Biochemical, and Endocrine Manifestations in Polycystic Ovary Syndrome

Pallavi Dubey [1,*], Ted Shi [2], Mallorie Coltharp [2] and Sireesha Reddy [1]

[1] Department of Obstetrics and Gynecology, Texas Tech University Health Sciences Center El Paso, El Paso, TX 79912, USA; sireesha.reddy@ttuhsc.edu
[2] Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center El Paso, El Paso, TX 79912, USA; ted.shi@ttuhsc.edu (T.S.); mallorie.coltharp@ttuhsc.edu (M.C.)
* Correspondence: paldubey@ttuhsc.edu

Abstract: Polycystic Ovary Syndrome (PCOS) is a reproductive, hormonal, and metabolic disorder frequently associated with insulin resistance, hyperandrogenism, chronic inflammation, and oxidative stress. Resveratrol is a naturally occurring polyphenolic stilbene found in trace amounts in some food items. It has been extensively used as a treatment option for metabolic disorders but its use in PCOS treatment has been limited. This review emphasizes the effect of resveratrol on the clinical features of PCOS, ovarian morphology, androgen profile, markers of oxidative stress, inflammatory markers, and metabolic markers associated with PCOS.

Keywords: Polycystic Ovary Syndrome; inflammation; resveratrol; ovarian morphology; insulin resistance; diet; treatment

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1. Introduction

Polycystic Ovarian Syndrome (PCOS) is noted for a phenotype of hyperandrogenism [1] and insulin resistance [2], as well as other metabolic sequelae. Hyperandrogenism [3] is the biochemical hallmark of PCOS. Excessive ovarian androgen levels are caused by increased androgen production by the ovarian theca cells. PCOS is associated with insulin resistance and weight gain in affected women [4], as well as abdominal obesity and difficulty with weight loss [5]. Additionally, PCOS puts women at a greater risk of health complications like diabetes, heart disease, hypertension, abnormal cholesterol levels, sleep apnea, stroke, depression, and anxiety. Insulin resistance can be found in 60–80% of women with PCOS with an increased prevalence of insulin resistance of 95% in obese women with PCOS [6]. The prevalence of obesity in women diagnosed with PCOS was determined to be 30% by Azziz et al. [7].

There is still a paucity of effective treatments for PCOS as the use of antiandrogens or suppression of ovarian function (e.g., by combination oral contraceptive [OC] pills) is often clinically unacceptable. There have been some alternate treatment approaches to reduce oxidative stress [8,9] and inflammation in PCOS, which mainly consist of nutritional supplementation and diet changes [10]. Treatment options remain limited; therefore, there is a need for an effective pharmaceutical therapy for the management of PCOS that avoids worsening, or potentially alleviates, other symptoms as well.

Resveratrol is a naturally occurring organic compound [11] synthesized by plants, functioning as a phytoalexin [12]. Phytoalexins are low molecular weight antimicrobial compounds that are produced by plants as a response to biotic and abiotic stresses. Resveratrol was first isolated in 1939 from the roots of the white hellebore and has since been extracted from numerous other plant sources such as apples, raspberries, blueberries, pistachios, plums, peanuts, and most commonly grapes [13]. However, due to resveratrol belonging to the class of polyphenols, there is a limited bioavailability of polyphenols in the body [14]. The oral absorption of resveratrol is about 75% by transepithilial diffusion.

Even after extensive metabolism in the intestine and liver results in the oral bioavailability considerably less than 1%. Dose escalation and repeated dosage, too, do not affect the bioavailability very much [15]. Metabolic studies have revealed that major metabolites of resveratrol are glucuronides and sulfates of resveratrol, which mainly enhance the resveratrol efficacy at the target sites [16]. Therefore, attempts are being made to introduce methylated analogs which may improve bioavailability [17].

Within the human body, resveratrol mediates a wide variety of physiological effects, such as prevention of free radical formation through antioxidant and platelet aggregation inhibitory properties; reduction of tumor growth through proapoptotic factors in addition to chemoprotective effects by reducing apoptotic potential of chemotherapy drugs on cell membranes and nucleic acids; immunomodulation by inducing IL-2 response and cytotoxic T cell production and promoting receptor–ligand interactions; and protective effects on the heart through anti-inflammatory factors. More recent studies on the physiological effects of resveratrol have explored the potential of antiaging and antidiabetic properties of the molecule [18]. Mouse models administered with resveratrol have shown an improvement in glucose homeostasis and insulin resistance [19]. Ovarian morphology was improved in terms of atretic and secondary follicles and the decreased number of Graafian follicles in the PCOS group after treatment with resveratrol. Resveratrol interacts with SIRT1 (silent information regulator1) expressed in oocytes and human granulosa nuclei cells at multiple developmental stages of the follicles [20].

Due to the perceived benefits of resveratrol from preclinical research, randomized clinical trials have been conducted by several groups in order to discover whether these effects could translate to clinical practice. In this narrative review, we examine sixteen recent randomized clinical trials to understand the pharmacological effect of resveratrol on humans diagnosed with PCOS or PCOS-induced rodent models.

2. Methods and Search Criteria for Markers and Treatment Strategies

Studies were chosen by searching PubMed for publications in English dating from 2008 to March 2022. Any randomized, placebo-controlled, double-blind trials, as well as systematic reviews and meta-analyses published from 2008 through 2022, were surveyed to review the literature published. Keywords used were clinical trial, RCT, resveratrol, PCOS, androgen excess, Polycystic Ovary Syndrome, and metabolic disorders. The studies were reviewed by all the authors. Opinions, letters to the editor, narrative reviews, and similar studies were excluded.

3. Inflammatory Markers

PCOS response can be measured by an increase in inflammatory markers and androgen levels. There are several markers that define PCOS variably expressed in different tissues. Interleukins (IL) have long been understood to be proteins involved in cellular and humoral responses to changes in the body—these cytokines modulate a wide variety of immune responses to maintain health (Table 1).

Table 1. Summary of studies done on human and rat models surveying effects of resveratrol supplementation.

Study Done by	Study Design	Subjects	Dose and Treatment Period	Area of Interest	Primary or Key Exploratory Outcomes	Secondary Outcomes
Effects of resveratrol on inflammatory markers						
Brenjian et al., 2020 [21]	Randomized, placebo-controlled trial	40 patients with PCOS	Resveratrol (800 mg/day) for 40 days	Effects of resveratrol on pro-inflammatory and edoplasmic reticulum stress markers in PCOS patients	Serum levels of IL-6, IL-1 beta, TNF-alpha, IL-18, NF-kbeta, CRp decreased.	Expression of ATF4, ATF6, GRP, CHOP, GRP78, XBP-1 increased.
Mansour et al., 2021 [22]	Randomized, placebo-controlled trial	78 patients with PCOS	Resveratrol (1000 mg/day) for 3 months	Effects of resveratrol on menstrual cyclicity, hyperandrogenism, and metabolic profile in PCOS	Improvement in menstruation rates and reduced hair loss.	No difference in adrenal and ovarian androgens or androgen index.
Liang et al., 2021 [23]	Experiemental study	PCOS induced rat models	Resveratrol (20 mg/kg/day) dissolved in 1% CMC for 30 days	Effects of resveratrol on follicular development	Decreased body weight, serum testosterone, and FSH.	Increased lactate and ATP, decreased pyruvate levels, upregulating LDHA, HK2, and PKM2. Upregulation of SIRT2.
Bahramrezaie et al., 2019 [24]	Triple-blind, randomized, placebo-controlled trial	62 patients with PCOS	Resveratrol (800 mg/day) for 40 days	Effects of resveratrol on angiogenesis pathway in PCOS	Reduction in the FSH, LH, TSH, and testosterone levels, as well as reduction in VEGF and HIF1 genes.	No significant difference in the number of mature oocytes, cleavage rate, fertilization rate, and fertility rate among the placebo and treatment groups, but the treatment group did have greater rates of high quality oocytes and high quality embryos.
Yarmolinskaya et al., 2021 [19]	Experimental study	Female Wistar rats with letrozole induced PCOS	Resveratrol (20 mg/kg/day or 30 mg/kg/day) for 30 days	Effectiveness of resveratrol as treatment for PCOS	Dose-dependent restoration of normal morphology of ovarian tissue, normalized regularity of estrous cycle, and decreased body weight.	

Table 1. *Cont.*

Study Done by	Study Design	Subjects	Dose and Treatment Period	Area of Interest	Primary or Key Exploratory Outcomes	Secondary Outcomes
Ghowsi et al., 2018 [25]	Case-control study	15 female Wistar rats split in 5 groups I) control, II) PCO-model-saline, III) PCO-model-resveratrol	Resveratrol (10 mg/kg/day) for 28 days	Effects of resveratrol on inflammatory marker expressions in PCOS rats	Tnf-α and Il-6 mRNA expression, when measured in adipocytes, were significantly decreased in the resveratrol-treated PCOS rats.	Inflammatory marker levels were not significantly different from the control rats not given any treatment.
Ashkar et al., 2020 [26]	Experimental study	70 adult female Sprague–Dawley rats randomly split in 7 groups	Group I) normal, II) vehicle, III) letrozole-induced PCOS, IV) PCOS induced receiving 150 mg/kg/day metformin, V) PCOS induced receiving 20 mg/lg/day resveratrol, VI) PCOS induced receiving 3 gr/kg/day barberry, VII) PCOS induced receiving 3 gr/kg/day barberry and 20 mg/kg/day resveratrol for 63 days	Effect of barberry and resveratrol on ovarian morphology and biochemical paramters in PCOS	Decrease in TNF-alpha levels and number of cystic follicles in groups that received resveratrol.	All groups receiving some form of treatment showed a decrease in IR and an increase in the SDA, TAC, and HDL levels.
Taheri et al., 2021 [27]	Randomized, placebo-controlled trial	Patients with PCOS (mean age 28.61 years (SD 4.99) and mean BMI 28.26 (SD 5.62)	Resveratrol (1000 mg/day) for 3 months	Effect of resveratrol on ovarian morphology in PCOS	Resveratrol treatment showed higher rate of improvement in the ovarian morphology, more dominant follicle count, and reduction in ovarian volume compared to placebo.	
Zhang et al., 2021 [28]	Case-control study	Sprague–Dawley rats split into 3 groups I) control, II) PCOS model, III) PCOS-resveratrol treatment	Resveratrol (40, 80, or 160 mg/kg/day) for 30 days	Phytoestrogenic effects of resveratrol on PCOS rat model	Increased levels of plasma adiponectin and estradiol levels and restoration of normal ovarian morphology.	

Table 1. *Cont.*

Study Done by	Study Design	Subjects	Dose and Treatment Period	Area of Interest	Primary or Key Exploratory Outcomes	Secondary Outcomes
Ergenoglu et al., 2015 [29]	Randomized, placebo-controlled trial	21 rat models split in 3 groups I) control, II) PCOS-placebo, III) PCOS-resveratrol	Resveratrol (10 mg/kg/day)	Effects of resveratrol on ovarian morphology, plasma AMH, IGF-1, and oxidative stress in PCOS rat models	Treatment significantly decreased plasma AMH and IGF1, lowered superoxide dismutase activity, and increased glutathione peroxidase.	Reduced antral follicle counts.
Rencber et al., 2018 [30]	Case-control study	63 female Wistar albino rats (54 with DHEA-induced PCOS, 9 control)	Resveratrol (20 mg/kg/day), metformin (300 mg/kg/day), or combined therapy for 35 days	Effects of resveratrol and metformin on ovarian reserve and ultrastructure in PCOS	Reduced serum testosterone, decreased LH, LH/FSH, TNF-α, and tissue AMH levels.	Ameliorated the elevated number of secondary and atretic follicles and the decreased number of Graafian follicles. Increased number of TUNEL (+) granulosa cells reduced significantly.
Banaszewska et al., 2019 [31]	Randomized, placebo-controlled trial	30 patients with PCOS	Resveratrol (1500 mg/day) for 3 months	Effects of resveratrol on PCOS	Significant decrease in total testosterone and DHEAS.	
Effects of resveratrol on insulin resistance						
Mansour et al., 2021 [22]	Randomized, placebo-controlled trial	78 females with PCOS	Resveratrol (1000 mg/day) for 3 months	Effect of resveratrol on menstrual cyclicity, hyperandrogenism, and metabolic profile in PCOS	No signicifcantly reduced adiposity.	No significant difference in insulin level, fasting blood glucose level, nor the HOMA-IR (insulin resistance index).
Benrick et al., 2013 [32]	Experimental study	PCOS-induced Wistar rat models	Resveratrol (400 mg/kg/day) with or without exercise for 5 days a week for 4 weeks, plus a 5th week of daily treatement	Comparing effects of resveratol and excercise on reproductive and metabolic function in PCOS induced rats	No significant change in insulin sensitivity or decrease in blood glucose levels.	Most significant decrease in adiposity was found in rats that were treated with resveratrol and allowed to exercise.
Banaszewska et al., 2019 [31]	Randomized, placebo-controlled trial	30 patients with PCOS	Resveratrol (1500 mg/day) for 3 months	Effects of resveratrol on PCOS	Significant decrease in insulin resistance.	No significant decrease in BMI nor fasting glucose.

Table 1. *Cont.*

Study Done by	Study Design	Subjects	Dose and Treatment Period	Area of Interest	Primary or Key Exploratory Outcomes	Secondary Outcomes
Ghowsi et al., 2018 [25]	Case-control study	15 female Wistar rats divided in 3 groups I) control group, II) PCO-placebo, III) PCO-resveratrol	Resveratrol (10 mg/kg/day) for 28 days	Effects of resveratrol on oxidative stress in the liver in PCOS	Resveratrol treated rats had a significant decrease in fasting serum glucose.	HOMO-IR and serum MDA decreased with resveratrol treatment.
Ashkar et al., 2020 [26]	Experimental study	70 adult female Sprague–Dawley rats randomly split in 7 groups	Group I) normal, II) vehicle, III) letrozole-induced PCOS, IV) PCOS induced receiving 150 mg/kg/day metformin, V) PCOS induced receiving 20 mg/lg/day resveratrol, VI) PCOS induced receiving 3 gr/kg/day barberry, VII) PCOS induced receiving 3 gr/kg/day barberry and 20 mg/kg/day resveratrol for 63 days	Effect of barberry and resveratrol on ovarian morphology and biochemical paramters in PCOS	Resveratrol treated rats exhibited significantly decreased insulin levels and HOMO-IR scores.	No significant difference amongst various treatments, suggesting all treatments are viable options.

Duleba et al. [33], in 2009, laid the foundations of the cascade of effects that arise from the low-grade inflammation that arises from a PCOS diagnosis. The group reviewed and theorized the upregulation of markers of tumor necrosis factor-alpha (TNF-alpha), interleukins IL-1 and IL-6, C-reactive protein (CRP), as well as erythrocyte sedimentation rate (ESR) in PCOS patients; TNF-alpha, IL-1, and IL-6 are the markers most responsible in generating a pro-inflammatory state. TNF-alpha is a cytokine secreted by white blood cells or macrophages to induce fever and the recruitment of WBCs. IL-6 is well known for its ability to increase the expression of acute-phase reactants to generate fever and the promotion of growth of WBC precursors to generate a larger immune response. IL-1 is also one of the widely recognized cytokines that promote fever, vasodilation, WBC chemotaxis, and transmigration. Drugs against all three of these factors are indicated in widely known chronic inflammatory conditions, such as arthritis [34] or Crohn's disease [35]. With the broadening of our knowledge on the inflammatory pathway, we have also come to understand how the cytokine cascade can lead to hyperandrogenism and insulin resistance as seen in PCOS. However, the use of anti-inflammatory agents can be non-specific and the side effects, such as immunosuppression, may outweigh the benefits for patients suffering from PCOS.

Current pharmacological interventions focus on reducing the effects of hyperandrogenism via the use of oral contraceptives, though this treatment may interfere with women who plan to conceive. Other symptomatic treatments include anti-androgens or the management of comorbidities, but none address the root cause of the disease. With there being no pharmacologically approved medications for PCOS patients, we wanted to gather experimental data to understand if resveratrol could be an appropriate therapy, due to previous work conducted in the preclinical setting. Therefore, our review indicated that resveratrol treatment more often significantly decreased markers of inflammation and androgens. In a 2019 study conducted by Brenjian et al. [21], the effects of treatment with resveratrol 800 mg/d/day for 40 days on PCOS-diagnosed women on serum inflammatory markers were evaluated. Serum levels of IL-6, IL-1beta, TNF-alpha, IL-18, NFkB, and CRP were found to be decreased with treatment. Ghowsi et al. [25] conducted a study in which PCOS-induced Wistar rats received resveratrol of 10 mg/kg, intraperitoneally induced in PCOS rats with increased lipid peroxidation and insulin resistance, and resveratrol improved these complications. The group found that the two markers, when measured in adipocytes, were significantly decreased in the resveratrol-treated PCOS rats compared to non-treated PCOS rats. These inflammatory marker levels were not significantly different from the control rats not given any treatment, suggesting that the resveratrol treatment returned the inflammatory marker expression levels to that of a healthy organism and may reduce inflammation caused by PCOS.

4. PCOS Markers including Hormones

In a 2018 study conducted by Rencber et al. [30], Wistar albino rats with dehydroepiandrosterone (DHEA)-induced PCOS and control rats were given resveratrol 20 mg/kg/day, metformin 300 mg/kg/day, and combined therapy for up to 35 days. The control group was found to have reduced body and ovary weights, reduced serum testosterone, and decreased LH, LH/FSH, TNF-alpha, and tissue AMH levels. In the PCOS group, there was found to be reduced serum testosterone, LH, LH/FSH, TNF-alpha, and tissue AMH levels (Table 1).

In this group, resveratrol was found to ameliorate the elevated number of secondary and atretic follicles and the decreased number of Graafian follicles. The increased number of TUNEL (+) granulosa cells were also reduced significantly with treatment. These results suggest that combined therapy of resveratrol and metformin has the most potential to improve weight gain and the hormone profile in PCOS patients, and to reduce inflammatory damage via SIRT1 and MAPK activation. Mansour et al. [22], conducted a randomized study on PCOS women ages 18–40 receiving either 1000 mg of resveratrol or 1000 mg of the placebo, daily, for a period of 3 months. The placebo and resveratrol treatment groups

had no difference in adrenal and ovarian androgens or androgen index, but the resveratrol treatment group did show improvement in menstruation rates and reduced hair loss.

Bahramrezaie et al. [24], conducted a triple-blind study in which 62 PCOS women received resveratrol at 800 mg/day or the placebo for 40 days, then analyzed FSH, LH, TSH, testosterone, and expression of VEGF and HIF1 genes. A reduction in the FSH, LH, TSH, and testosterone levels, as well as a reduction in VEGF and HIF1 genes, were noted in those that received resveratrol. There was not a significant difference in the number of mature oocytes, cleavage rate, fertilization rate, and the fertility rate among the placebo and resveratrol groups, but the resveratrol group did have greater rates of high-quality oocytes and high-quality embryos, suggesting that resveratrol may improve outcomes for some PCOS patients.

In the study conducted by Liang et al. [23], letrozole and high-fat diet-induced PCOS rats were administered resveratrol at 20 mg/kg/day, dissolved in 1% CMC administered orally for 30 days. Decreased body weight, serum testosterone, and FSH were recorded. Increased serum lactate and ATP with decreased pyruvate levels upregulated LDHA, HK2, and PKM2. There was also upregulation of SIRT2. These results suggested that resveratrol suppressed damage to the ovaries in PCOS by restoring glycolytic activity.

In a study conducted by Yarmolinskaya et al. [19], letrozole-induced PCOS Wistar rats received resveratrol at 20 mg/kg and 30 mg/kg doses for 30 days. Resveratrol was found to have dose-dependent effects on the normalization of ovarian tissue morphology, regularity of estrous cycle, and decreased bodyweight, suggesting that it may be a useful therapeutic option for the treatment of PCOS.

In a study conducted by Taheri et al. [27], the effects of treatment with resveratrol at 1000 mg or the placebo for 3 months in PCOS women with a mean age of 28.61 years (SD 4.99) and a mean BMI of 28.26 (SD 5.62) were compared. The women receiving resveratrol treatment were shown to have a higher rate of improvement in ovarian morphology, a more dominant follicle count, and more reduction in ovarian volume than the placebo group, which did not show any significant changes.

Zhang et al. [28] conducted a study with letrozole-induced PCOS female Sprague–Dawley rats organized into groups: control, resveratrol at a 40 mg/kg treatment, resveratrol at an 80 mg/kg treatment, and resveratrol at a 160 mg/kg treatment. After 30 days, ovarian tissues were collected and analyzed. Resveratrol treatment was determined to be associated with increased plasma levels of adiponectin and estradiol, restoration of normal ovarian morphology, and increased expression of nesfatin-1 and aromatase at RNA and protein levels.

In a study conducted by Banaszewska et al. [31], PCOS women were given either resveratrol at 1500 mg by mouth, daily, or a placebo for 3 months. The placebo group was found to have unaltered gonadotropins, markers of inflammation, and endothelial function, while those that received resveratrol had a significant decrease in total testosterone and DHEAS.

In conclusion, with the use of resveratrol, changes in ovarian morphology were observed, and in a few patient trials, there was a slight improvement in the androgen homeostasis, while animal models showed better improvement rates in term of ovarian morphology and hormone balance.

5. Metabolic Markers and Insulin Resistance

Since insulin resistance is a hallmark of PCOS progression, studies that examine the effect of resveratrol on metabolism in an attempt to reverse the negative effects of PCOS include gathering data on the glycoinsulinemic index, lipid profile, and/or body composition. In the studies, we found resveratrol either had no effect or decreased insulin resistance in PCOS subjects or rats, though more experimentation is needed to determine why some experimental groups responded favorably to resveratrol treatment while others had no effect (Table 1).

Clinical traits for PCOS include weight gain, insulin resistance, and incidence of type II diabetes, but very few pharmaceutical interventions have been effective in treating this aspect. Metformin has been described as a potential treatment, though the medication itself may cause menstrual irregularity, and its effects continue to be studied. Current literature suggests that the pathway for the pathogenesis and progression of PCOS is shared with those involved in increased adiposity through metabolic pathways in muscle and fat. We aim to understand if resveratrol is able to fill the pharmacological role in reversing the effects in signaling abnormalities previously theorized. Currently, the clinical recommendation for women diagnosed with PCOS continues to be physical exercise and dietary changes, with few pharmacological interventions available for these women.

In 2020, Ashkar et al. [26], conducted a study with seventy adult female Sprague–Dawley rats randomly divided into seven groups: normal, vehicle, letrozole-induced PCOS receiving 1 cc of normal saline orally, PCOS receiving 150 mg/kg of metformin orally, PCOS receiving 20 mg/kg of resveratrol orally, PCOS receiving 3 gr/kg of barberry orally, and PCOS receiving 3 gr/kg of barberry and 20 mg/kg of resveratrol orally. There was no significant difference in the serum glucose levels in the treatment groups, but the resveratrol groups (with or without barberry) showed a decrease in LDL, TG, MDA, and TNF-alpha levels, and a decrease in the number of cystic follicles. All groups receiving some form of treatment showed a decrease in IR and an increase in the SDA, TAC, and HDL.

The clinical data described on reversing insulin resistance have been variable. In the study conducted by Mansour et al. [22], when human subjects were given resveratrol at 1000 mg, daily, for 3 months compared to a placebo, the resveratrol treatment group did not have significantly reduced adiposity. Furthermore, the study did not note a significant difference in insulin level, fasting blood glucose level, nor the HOMA-IR (insulin resistance index) between the two groups after 3 months.

Benrick et al. [32], compared the effects of resveratrol at 400 mg/kg/day on dihydrotest osterone-induced PCOS rats which were either sedentary or allowed to exercise. When compared to vehicle and control groups, treatment alone with resveratrol did not show a statistically significant decrease in insulin sensitivity compared to those that were also allowed to exercise. The blood glucose levels also did not differ between the experimental and control groups. When measuring the adiposity of rats after treatment, the most significant decrease in adiposity was in rats who were given the resveratrol and allowed to exercise. However, the authors note that there was also a significant difference in adiposity between the resveratrol only and the vehicle only groups.

In the study conducted by Banaszewska et al. [31], human subjects diagnosed with PCOS were given either resveratrol at 1500 mg by mouth, daily, or a placebo for 3 months. Despite not seeing a significant difference in BMI nor the fasting glucose level, the authors reported a significantly lowered fasting insulin level and a significantly increased insulin sensitivity index.

In a study conducted by Ghowsi et al. [25], PCOS-induced rats in the experimental group were given resveratrol at 10 mg/kg intraperitoneal injections for 28 days. The fasting serum glucose levels significantly decreased in the resveratrol-treated PCOS rats compared to the PCOS-control rats. Furthermore, the HOMA-IR index showed a significant decrease in insulin resistance in resveratrol-treated rats compared to the PCOS control. This study suggested that resveratrol had played a role in decreasing insulin resistance.

In the study by Ashkar et al. [26] described above, resveratrol-treated rats with induced-PCOS exhibited significantly decreased insulin levels and HOMO-IR scores. However, there were no significant differences in the various treatment groups, suggesting that all treatments were effective in reducing insulin resistance in these model rats.

6. Markers of Oxidative Stress

In a study conducted by Ergenoglu et al. [29], dihydrotestosterone-induced PCOS rats were randomly divided and received either 1 mL/kg/day of isotonic saline, or 10 mg/kg/day of resveratrol. The resveratrol group was found to have reduced antral

follicle counts and significantly decreased plasma AMH and IGF1, as well as reduced superoxide dismutase activity and increased glutathione peroxidase, suggesting that the antioxidant properties of resveratrol allow for it to be an effective treatment for PCOS. Ashkar et al. [26] also looked at the MDA and TAC levels in letrozole-induced PCOS rats and found an increase in the SDA and TAC levels overall. Ghowsi et al. [25] found resveratrol group had higher levels of liver MDA in PCOS-induced Wister rats (Table 1).

7. Discussion

Resveratrol has been extensively used for the treatment of metabolic abnormalities, atherosclerosis, coronary artery disease, diabetes, and inflammation. Since PCOS is closely associated with diabetes and metabolic abnormalities, researchers have been trying to find the alternative treatment of PCOS through resveratrol alone or in combination with other supplements. Most of the RCTs have been done on the PCOS-induced rat models, so there is still insufficient data on human subjects. While resveratrol seemed to be an effective approach in rat models, human trials did not seem to show significant improvements in terms of gonadotropin levels, lipid profiles, markers of inflammation, and endothelial function.

In two studies, the authors observed a marked difference in reduction in ovarian volume and an improvement in ovarian morphology, but only slight-to-no difference was observed in adrenal and ovarian androgens. In rat models, however, a significant difference in oxidative stress markers, inflammatory markers, and androgens was observed. Fasting insulin levels were decreased with an increased insulin sensitivity index in most studies. Resveratrol in combination with barberry extract administered orally was very effective in decreasing the lipid markers and androgens and improving the oxidative stress markers. A study by Bernick [32] was, however, contradictory to the RCTs, where the exercise was proven more effective in improving insulin sensitivity and estrous cyclicity.

8. Limitations

Our review has addressed concerns regarding the use of resveratrol in PCOS treatment. However, our review has some limitations. Most of the RCTs were performed on PCOS rat models and the trials on human subjects suffer from small sample sizes. These shortcomings, as well as the variable and limited bioavailability of resveratrol, makes it difficult to interpret if the cause of an RCT with neutral results is due to dosing and/or sample size, or general lack of potency of natural resveratrol (potentially fixed through chemical techniques/analogs).

9. Conclusions

In conclusion, resveratrol was found to be more effective in rat models and in alleviating markers of oxidative stress and ovarian morphology, but less effective in insulin sensitivity and decreasing androgen profile.

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