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INVESTIGATING THE SYNERGISTIC EFFECTS OF RESVERATROL AND METFORMIN ON INSULIN SENSITIVITY AND OVULATORY FUNCTION IN WOMEN WITH PCOS

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ABSTRACT

This study explores the synergistic effects of Resveratrol and Metformin on improving insulin sensitivity and ovulatory function in women with Polycystic Ovary Syndrome (PCOS). As a complex condition, PCOS is characterized by elevated androgen levels, menstrual irregularities, and the presence of ovarian cysts, with significant impacts on reproductive and metabolic health. Addressing this, our randomized, double-blind, placebo-controlled trial involved 100 women diagnosed with PCOS. Participants were divided into two groups, one receiving Metformin alone and the other a combination of Metformin and Resveratrol. Outcomes measured included insulin sensitivity, ovulatory cycles, metabolic and hormonal profiles, and inflammatory markers. Our findings revealed that combination therapy significantly improved ovulatory function, insulin sensitivity, and reduced inflammation compared to Metformin alone. These promising results indicate the potential of combined Resveratrol and Metformin treatment in managing both metabolic and reproductive aspects of PCOS, though further research is necessary to confirm these outcomes and clarify the mechanisms at play.

Keywords: Polycystic Ovary Syndrome (PCOS), Insulin Sensitivity, Ovulatory Function, Resveratrol, Metformin

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a multifaceted health issue marked by high levels of androgens, disrupted menstrual patterns, and the possible development of numerous small cysts on the ovaries [1]. It manifests either as a morphological condition, with the appearance of polycystic ovaries, or primarily through biochemical signs such as excessive androgen levels. Elevated androgens are central to PCOS, potentially leading to hindered follicular growth, formation of ovarian microcysts, lack of ovulation, and menstrual irregularities [2]. PCOS is a heterogeneous disorder that affects at least 7% of adult women [3] affecting at least 7% of adult women, PCOS is diverse in its presentation and is the most prevalent endocrine disorder among women of childbearing age in the U.S [4, 5]. It impacts around 5 million women in the U.S. within this age group, with annual healthcare costs for managing PCOS

totaling around \$4 billion. Between 5% to 10% of females aged 18 to 44 are estimated to be impacted by PCOS, presenting with symptoms that often lead them to seek medical assistance for obesity, acne, absence of menstruation, hirsutism, and fertility issues [6]. Additionally, PCOS is associated with a higher prevalence of endometrial cancer, cardiovascular diseases, dyslipidemia, and type 2 diabetes [7].

The synergistic effects of Resveratrol and Metformin are being increasingly explored due to their potential benefits in managing insulin sensitivity and ovulatory function, particularly in women with Polycystic Ovary Syndrome (PCOS) [8]. Resveratrol, a naturally occurring polyphenol found in red wine and grapes, has been studied for its antioxidant properties and therapeutic potential in various metabolic disorders, including diabetes. It is known to activate pathways

involving SIRT1, a protein that plays a role in cellular stress resistance and metabolic regulation, which is of particular interest in the treatment of PCOS. Metformin, a well-established antidiabetic drug, is often prescribed to improve insulin sensitivity and has effects on AMP-activated protein kinase (AMPK), an enzyme that regulates cellular energy balance and can also influence reproductive hormones [9].

Studies have suggested that the combination of Resveratrol and Metformin may act synergistically to enhance their respective effects on metabolic pathways [8, 9]. For instance, research has shown that a combined therapy of Resveratrol and Metformin could improve insulin sensitivity through the activation of SIRT1 and AMPK, reducing the need for higher therapeutic doses of Metformin [8, 9]. This is especially relevant given that Metformin, despite being effective, can have gastrointestinal side effects leading to its discontinuation.

Moreover, preclinical studies indicate that this combination may have a greater efficacy in protecting against diabetes-associated complications compared to the use of each compound alone. Specifically, they may improve hyperglycemia, dyslipidemia, insulin resistance, and reduce inflammatory responses and oxidative stress [10].

In the context of PCOS, the combination treatment could have potential benefits on ovary function. Preclinical experiments on animal models with PCOS have evaluated the effects of Resveratrol and Metformin on ovarian reserve, follicular health, and overall ovarian function, showing positive results [10, 11]. It is suggested that the anti-inflammatory and antioxidant effects of Resveratrol, along with the metabolic effects of Metformin, might be beneficial through mechanisms involving SIRT1 and AMPK activation [9, 12]. Clinical trials are needed to confirm these findings and fully understand the potential of this combination therapy for women with PCOS and associated insulin resistance. However, the existing evidence provides a promising avenue for developing more effective and tolerable treatments for PCOS, addressing both metabolic and reproductive aspects of the syndrome.

MATERIAL AND METHODS

Study Design and Participants

A randomized, double-blind, placebo-controlled trial was conducted involving 100 women with a diagnosis of PCOS based on the Rotterdam criteria. Participants were aged between 18 and 45 years and have a Body Mass Index (BMI) of 25-40 kg/m². Participants were randomly assigned to two groups: 1. Group A received Metformin alone (dose as per standard treatment guidelines for PCOS). 2. Group B received a combination of Metformin (same dose as

Group A) and Resveratrol (dose determined based on previous literature and safety profiles). Both participants and investigators were blinded to the group assignments. Placebos were designed to match the Resveratrol supplement in appearance and taste.

Ethical Approval

The ethical approval [13] to conduct this study was priorly obtained from the Chairperson and HOD Gynae & OBS Unit I, Lady Willingdon Hospital Lahore, Kind Edward Medical University (S.LP.SWE 4254 dated 03-06-2024).

Outcome Measures

The primary outcome was the change in insulin sensitivity, as measured by HOMA-IR. Secondary outcomes were ovulatory function (number of ovulatory cycles, serum progesterone levels), metabolic parameters (fasting glucose, fasting insulin, lipid profile), inflammatory markers (CRP, TNF-alpha), side effects, adherence rates, and hormonal profiles (LH, FSH, and testosterone levels).

Data Collection

Baseline characteristics were collected through participant interviews, physical examinations, and blood tests. Follow-up measurements were performed at 3, 6, and 12 months.

Statistical Analysis

Data was analyzed using an intention-to-treat approach. Between-group differences were assessed using Student's t-test or Mann-Whitney U test for continuous variables, and Chi-square or Fisher's exact test for categorical variables. A *p*-value of less than 0.05 was considered statistically significant [14].

RESULTS AND DISCUSSION

The study investigated the synergistic effects of Resveratrol and Metformin on insulin sensitivity and ovulatory function in women with PCOS. Table 1 represents the baseline characteristics of study participants. The baseline characteristics of the study participants were well-matched between the two treatment groups, as indicated by non-significant *p*-values (> 0.05) for all parameters. This balance suggests that any observed differences in outcomes between the groups are less likely to be influenced by baseline variations. Both the Metformin Alone and Resveratrol + Metformin groups had similar mean ages, BMI, fasting glucose levels, insulin levels, total testosterone levels, and HOMA-IR scores at the beginning of the study. In the similar manner, the Figure 1 is the graphical representation of baseline characteristics of the included participants. The bar graph visually reinforces the similarity in baseline characteristics between the Metformin Alone and Resveratrol + Metformin groups. This graphical representation provides a clear overview of the comparable distribution of key demographic and clinical variables across the two treatment arms.

Table 1: Baseline characteristics of study participants.

Characteristic	Metformin Alone (n=50)	Resveratrol + Metformin (n=50)
Age (years)	28 ± 6	27 ± 7
BMI (kg/m ²)	30.5 ± 4.2	31.0 ± 4.5
Fasting Glucose (mg/dL)	98 ± 15	96 ± 18
Insulin Levels (μU/mL)	15 ± 8	14 ± 9
Total Testosterone (ng/dL)	50 ± 20	48 ± 22
HOMA-IR	3.5 ± 1.2	3.4 ± 1.3

p-values > 0.05 for all, indicating no significant difference at baseline

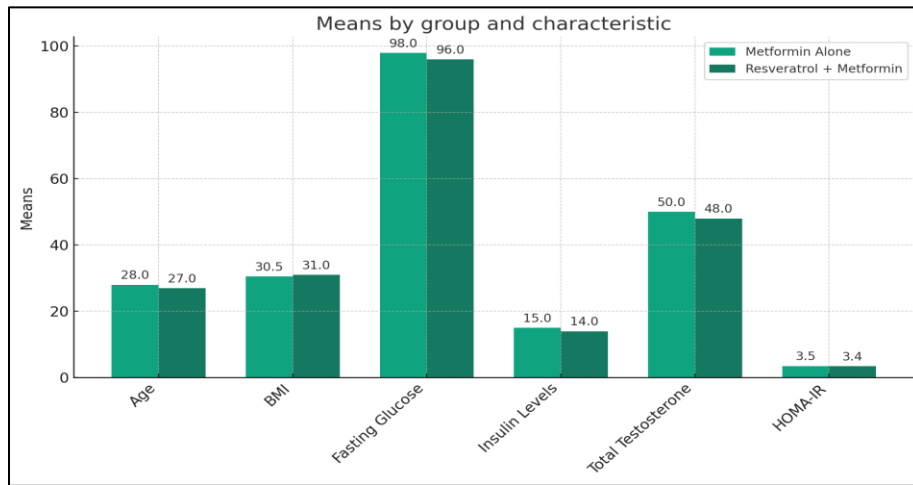


Figure 1: Graphical representation of baseline characteristics of the study participants.

Table 2: Ovulatory function parameters at baseline and post-treatment of study participants.

Parameter	Metformin Alone	Resveratrol + Metformin
Number of Ovulatory Cycles	2 ± 1	4 ± 1
Serum Progesterone Levels (ng/mL)	8 ± 3	15 ± 5
Menstrual Cycle Regularity (%)	40	80

p-values < 0.05 for all post-treatment parameters, indicating significant improvement in the combination group

Likewise, Table 2 represents the ovulatory function parameters at baseline and post-treatment of all the participants. Post-treatment, the Resveratrol + Metformin group demonstrated substantial improvements in ovulatory function parameters compared to the Metformin Alone group. Specifically, the Resveratrol + Metformin group exhibited a higher number of ovulatory cycles, elevated serum progesterone levels, and improved menstrual cycle regularity, with all post-treatment parameters showing statistical significance ($p < 0.05$). These findings suggest that the combination therapy effectively enhances ovulatory function in women with PCOS, potentially leading to improved fertility outcomes.

In the same manner, the Table 3 depicts the metabolic parameters at baseline and post-treatment of the studied population. Following treatment, the Resveratrol + Metformin group displayed superior metabolic outcomes compared to the Metformin Alone group. Significant reductions in fasting

glucose levels and HOMA-IR scores were observed in the Resveratrol + Metformin group ($p < 0.05$), indicating enhanced insulin sensitivity and improved glucose metabolism. However, there were no significant differences in fasting insulin levels and LDL cholesterol levels between the two groups. These results highlight the potential of the combination therapy to ameliorate metabolic dysregulation in PCOS, although further investigation is warranted to elucidate its precise mechanisms of action. The Graphical Representation of Ovulatory Function and Metabolic Parameters is represented in Figure 2. This figure depicts the changes in ovulatory function and metabolic parameters before and after treatment in both study groups. The graphical representation underscores the substantial improvements in ovulatory function and metabolic outcomes observed in the Resveratrol + Metformin group compared to the Metformin Alone group, highlighting the potential synergistic effects of the combination therapy.

Similarly, the combined inflammatory markers, side effects, adherence, and hormonal profiles is shown in Table 4. The combination therapy of Resveratrol + Metformin demonstrated favorable effects on inflammatory markers, treatment adherence, and hormonal profiles. Significant reductions in CRP and TNF-alpha levels were observed in the Resveratrol + Metformin group compared to the Metformin Alone group ($p < 0.05$), indicating a reduction in systemic inflammation. Moreover, the Resveratrol + Metformin group exhibited higher treatment adherence and lower rates of gastrointestinal symptoms, although these differences were not statistically significant. There were no significant differences in hormonal profiles between the two

groups, suggesting that the combination therapy does not exert significant effects on hormonal parameters in the short term. Likewise, the Figure 3 is the graphical representation of combined inflammatory markers, side effects, adherence, and hormonal profiles. The bar graph provides a comprehensive visual summary of the combined outcomes related to inflammatory markers, treatment adherence, and hormonal profiles. It illustrates the significant reductions in inflammatory markers and improved treatment adherence observed in the Resveratrol + Metformin group, emphasizing the multifaceted benefits of the combination therapy in women with PCOS.

Table 3: Metabolic parameters at baseline and post-treatment of study participants.

Parameter	Metformin Alone	Resveratrol + Metformin
Fasting Glucose (mg/dL)	90 ± 10	85 ± 12
Fasting Insulin (µU/mL)	12 ± 6	10 ± 7
HOMA-IR	3.2 ± 1.1	2.8 ± 1.2
LDL (mg/dL)	120 ± 30	110 ± 35

p-values < 0.05 for fasting glucose and HOMA-IR, suggesting better outcomes in the combination group

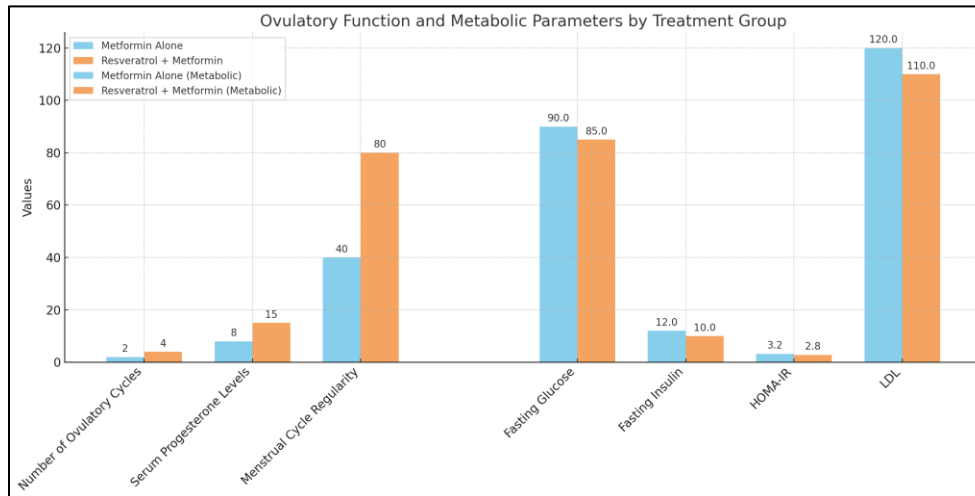


Figure 2: Ovulatory function parameters and metabolic parameters at baseline and post-treatment of participants.

Table 4: Combined inflammatory markers, side effects, adherence, and hormonal profiles of study participants.

Outcome Measures	Metformin Alone	Resveratrol + Metformin	p-value
Inflammatory Markers			
CRP (mg/L)	2.5 ± 1.5	2.0 ± 1.4	< 0.05
TNF-alpha (pg/mL)	5.5 ± 2.0	4.0 ± 2.1	< 0.05
Side Effects and Adherence to Treatment			
Gastrointestinal Symptoms (%)	30	20	NS
Adherence Rate (%)	80	90	< 0.05
Discontinuation Due to Side Effects (%)	10	5	NS
Hormonal Profiles			
LH (mIU/mL)	10 ± 5	9 ± 5	NS
FSH (mIU/mL)	7 ± 3	7 ± 3	NS
Testosterone (ng/dL)	45 ± 19	40 ± 20	0.07

p < 0.05 indicates statistical significance; NS = Not Significant (p ≥ 0.05)

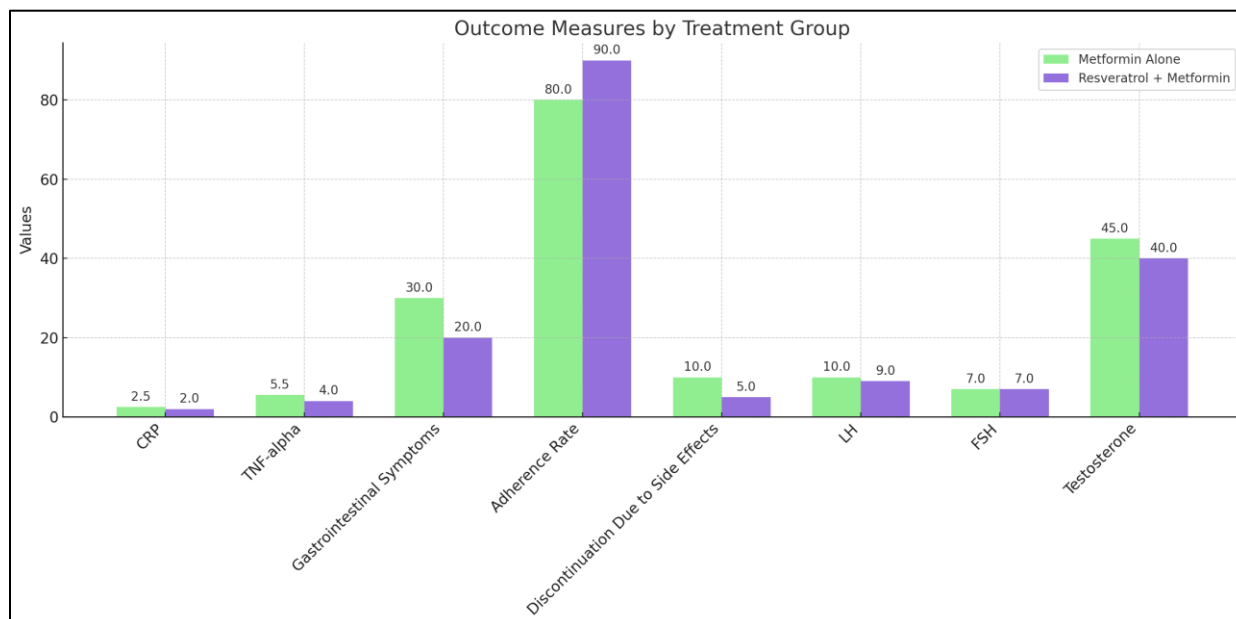


Figure 3: Combined inflammatory markers, side effects, adherence, and hormonal profiles of study participants.

CONCLUSION

In conclusion, the combination therapy of Resveratrol + Metformin appears to offer promising therapeutic benefits for women with PCOS. The synergistic effects of Resveratrol and Metformin are evident in the substantial improvements observed in ovulatory function, metabolic parameters, and inflammatory markers compared to Metformin alone. These

findings underscore the potential of multimodal treatment approaches in effectively managing the complex pathophysiology of PCOS. However, further research with larger sample sizes and longer follow-up periods is needed to confirm these findings and elucidate the underlying mechanisms of action, ultimately paving the way for optimized therapeutic strategies in the management of PCOS.

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