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Therapeutic Effect of Methanolic Extract of *Nelumbo nucifera* Leaves against Letrozole - Induced Polycystic Ovary Syndrome in Female Rats

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Abstract

Background: The most prevalent endocrine condition, Polycystic Ovary Syndrome (PCOS), is characterised by polycystic ovarian morphology, hyperandrogenism, and ovarian dysfunction. Anti-angiogenic, anti-cancer, anti-diabetic, anti-obesity, anti-inflammatory, antioxidant, anti-microbial, hepatoprotective, and anti-hyperlipidemic properties are just a few of the pharmacological activities of *N. nucifera*. **Aim:** The purpose of the study is to look at the potential benefits of a methanolic extract of *Nelumbo nucifera* leaves (MENN) in treating PCOS brought on by letrozole. **Methods:** Letrozole was administered for 21 days to develop PCOS, and vaginal smear surveillance was used to validate the condition. Both low-dose (250 mg/kg) and high-dose (500 mg/kg) MENN were administered to PCOS rats. A histological evaluation was conducted after estimating the serum glucose, testosterone, lipid profile, and antioxidant enzymes in the ovaries, such as superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), and malondialdehyde (MDA). **Results:** According to the findings, MENN raised HDL levels while lowering serum glucose, testosterone, total cholesterol, triglycerides, LDL, and VLDL levels. Additionally, it lowered MDA levels and raised ovarian antioxidant enzymes like SOD, catalase, and GSH. By raising the amount of corpus luteum and follicles, decreasing the number of cysts, and minimising endometrial hyperplasia, MENN improved the histological abnormalities in the uterus and ovaries. The levels of parameters impacted by letrozole treatment were restored by MENN. **Conclusion:** By lowering androgen levels and normalising glucose, lipid profiles, and antioxidants, MENN had a preventive effect against PCOS through a regular oestrous cycle, according to the data.

Major Findings: Methanolic extract of *Nelumbo nucifera* leaves was found to have a protective effect against PCOS through antihyperglycemic, antihyperlipidemic, antioxidant and normalisation of histological abnormalities in ovaries and uterus.

Keywords: Blood Glucose, Blood Testosterone, Ovarian Cysts, Ovarian Antioxidants, Phytotherapy

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1. Introduction

One of the most prevalent and intricate endocrine conditions that causes infertility in women is PCOS[1]. Hormonal imbalance, metabolic abnormalities, and ovarian malfunction are the hallmarks of this diverse illness[2]. Worldwide, 4–10% of women of reproductive age are suffering from PCOS[3]. PCOS is

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a complex condition with a wide range of underlying pathophysiology and clinical features. PCOS can be treated with drugs, but not all women respond well to them, and some people may experience unfavourable side effects. Nowadays, the most often used medications to treat PCOS are tamoxifen, metformin, and clomiphene citrate. According to studies, long-term usage of these medications may result in gastrointestinal side effects, nephrotoxicity, hot flashes, pregnancy difficulties, and tubular vacuolization[4]. Because of the previously mentioned drawbacks of traditional therapy, people are becoming more interested in herbal remedies. Herbal treatments for PCOS are highly successful in lowering obesity and hyperandrogenism while also enhancing ovulation and insulin sensitivity[5]. *N. nucifera* is a traditional medicine that contains a lot of powerful flavonoids that have a variety of useful pharmacological effects[6]. Leaf extracts of *N. nucifera* have shown several pharmacological activities, including but not limited to ameliorating hyperlipidemia, stimulating insulin secretion, inducing vasodilation, reducing blood pressure, and demonstrating anti-arrhythmic properties[7]. Hence, the present study aims to assess the *in vivo* therapeutic impact of a methanolic extract of *N. nucifera* leaves against PCOS in female rats.

2. Materials and Methods

2.1 *Nelumbo nucifera* Leaf Extraction

Methanolic extract of *N. nucifera* leaves was procured from Ayushagro Food, Dilshad Garden Industrial Area, Dilshad Garden, New Delhi.

2.2 Experimental Animals

Adult female albino Wistar rats weighing 150–180 g and 1.5 months of age were acquired from Mahaveer Rat Enterprises, Hyderabad, and animals were maintained as per the Committee for Control and Supervision of Experiments on Animals (CCSEA). The protocol was approved by the institutional animal ethical committee (IAEC/IV/06/RIPER/2024).

2.3 Dose Selection

LD_{50} value for the methanolic extract of *N. nucifera* was found to be more than 2000mg/kg according to OECD guideline 425. Hence, $1/8^{th}$, $1/4^{th}$ of 2000 mg/kg, i.e, 250mg/kg, 500mg/kg were selected for evaluation against PCOS in rats[8].

2.4 Induction of PCOS

The rats were given letrozole orally at a dose of 1 mg/kg body weight once a day for 21 days to induce PCOS.

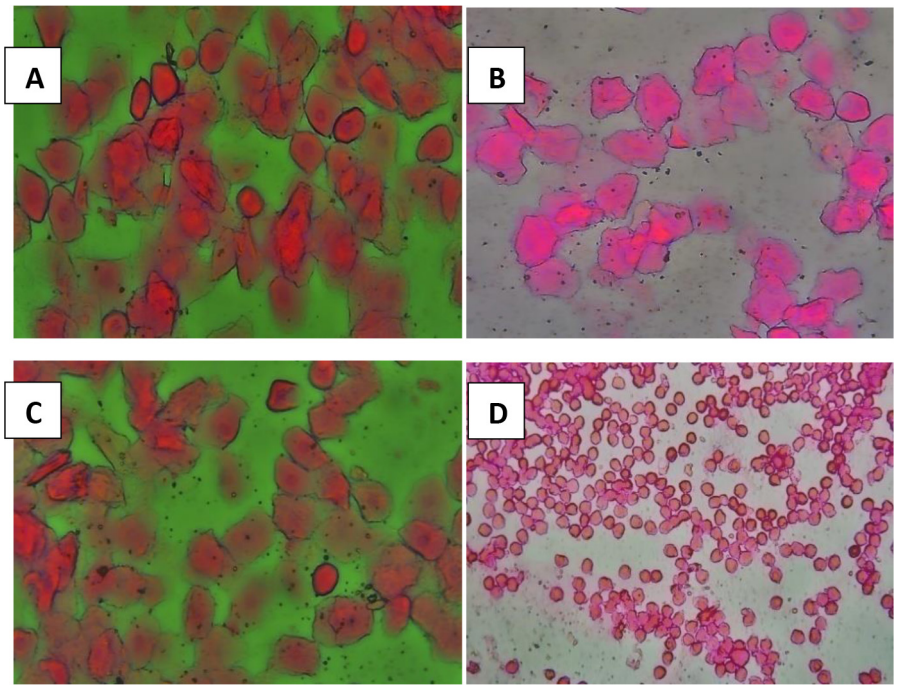


Figure 1. Vaginal smears of rats – **(A).** Proestrous phase, **(B).** Oestrous phase, **(C).** Metaestrous phase and **(D).** Diestrous phase.

The rats were then exposed to vaginal smear tests every day to verify the development of PCOS. By examining the irregularity of the oestrous cycle and the presence of chronic vaginal cornification under a microscope, the induction of PCOS was verified[9] (Figure 1).

2.5 Experimental Design

Five groups of six albino Wistar females, each with a normal oestrous cycle, were randomly selected from a total of thirty mature adult rats. Group 1 (normal control group) was given an oral dose of 0.5% CMC, while Group 2 (PCOS-induced group) received letrozole orally at a dose of 1 mg/kg body weight. Group 3 (Metformin): PCOS rats were given 250 mg/kg body weight of metformin via the oral route for a month. Group 4 (MENN 250mg/kg): For one month, PCOS rats were given an oral dose of 250 mg/kg body weight of the methanolic extract of *N. nucifera* leaves. Group 5 (MENN 500mg/kg): For one month, PCOS rats were given an oral dose of 500 mg/kg body weight of the methanolic extract of *N. nucifera* leaves.

Following the course of treatment, the body weights of all animals were recorded and sedated with xylazine and ketamine. A retro-orbital puncture was used to obtain the blood samples, and centrifugation at 3500 rpm was used to extract the serum. The resulting serum was utilised to estimate glucose, lipid parameters, and hormones (using an ELISA kit for testosterone) using commercially available assays. Following the rats' euthanasia, the ovaries were removed in order to measure the antioxidant indices SOD, CAT, GSH, and MDA[10].

2.6 Histomorphology

Rats' uteri and ovaries were separated, and the attached connective adipose tissue was extracted. After that, 10% v/v formalin was used to fix the uterine and ovarian tissues. Standard procedures were followed for preparing the tissue. After being dehydrated, the samples were embedded in paraffin wax and cut with a rotary microtome into slices that were 5µm thick. Hematoxylin and eosin were used to stain the produced slices in order to make histological findings. The fluorescence microscope was used to view the slides.

2.7 Statistical Analysis

The software Graph Pad Prism 10.2.3 (397) was used to do the statistical analysis. Mean ± SEM was used to present the data. Post hoc test was used after one-way Analysis of Variance (ANOVA) to assess statistical significance and group differences.

3. Results

3.1 MENN's Impact on Rats' Body Weights

When rats were given letrozole for 21 days to induce PCOS, their body weight significantly increased compared to the normal group ($P<0.001$). Rats given 250 mg/kg of MENN demonstrated a substantial reduction in body weight as compared to the PCOS group ($P<0.05$). Rats given 500 mg/kg of MENN demonstrated a substantial reduction in body weight as compared to the PCOS group ($P<0.01$) (Table 1).

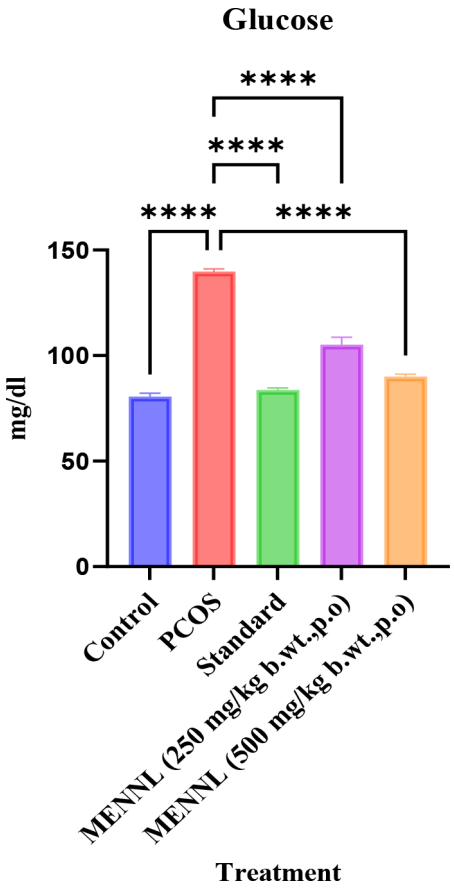
3.2 Impact of MENN on Rats' Blood Glucose Levels

When compared to the control group, the PCOS rats' serum glucose levels were considerably higher ($P<0.001$). Serum glucose levels in rats treated with MENN at a dose of 250 mg/kg were significantly lower ($p<0.05$) than in the PCOS rats. Rats given 500 mg/kg of MENN showed a substantial reduction in glucose

Table 1. Effect of MENN on the body weight (g) of the rats

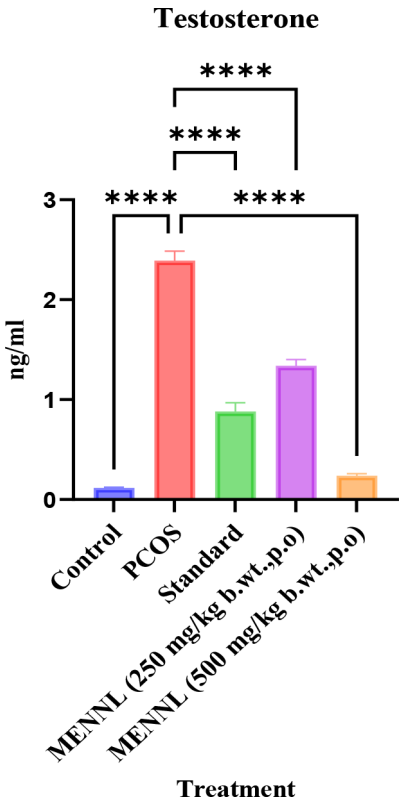
Group	Initial	After induction	After treatment
Control	148±0.37	159±0.41	169±0.48
PCOS	142±0.35	200±2.67	210±3.68[a]
Metformin	130±0.25	195±2.25	145±0.32[b]
MENN (250mg/kg)	145±0.32	198±2.32	172±0.45[c]
MENN (500mg/kg)	135±0.28	205±2.85	146±0.32[b]

Data represent mean ± SEM. [a]$P<0.001$ versus control group, [b]$P<0.001$, [c]$P<0.05$ versus PCOS induced group (One way ANOVA followed by Tukey's Post - hoc test)



Data represent mean ± SEM. ***P<0.001 versus control group, ***P<0.001 versus PCOS group (One-way ANOVA followed by Tukey's Post hoc test).

Figure 2. Effect of MENN on blood glucose levels.



Data represent mean ± SEM. ***P<0.001 versus control group, ***P<0.001 versus PCOS group (One-way ANOVA followed by Tukey's Post hoc test).

Figure 3. Effect of MENN on blood testosterone levels.

levels when compared to the PCOS rats (P<0.001) (Figure 2).

3.3 Impact of MENN on Rats' Blood Testosterone Levels

When compared to the control group, the PCOS rats' serum testosterone levels were considerably higher (P<0.001). Serum testosterone levels were significantly lower in rats treated with MENN at a dose of 250 mg/kg than in the PCOS group (P<0.05). Rats treated with MENN at a dose of 500 mg/kg showed significantly lower testosterone levels than the PCOS rats (P<0.01) (Figure 3).

3.4 Impact of MENN on Rats' Blood Total Cholesterol Levels

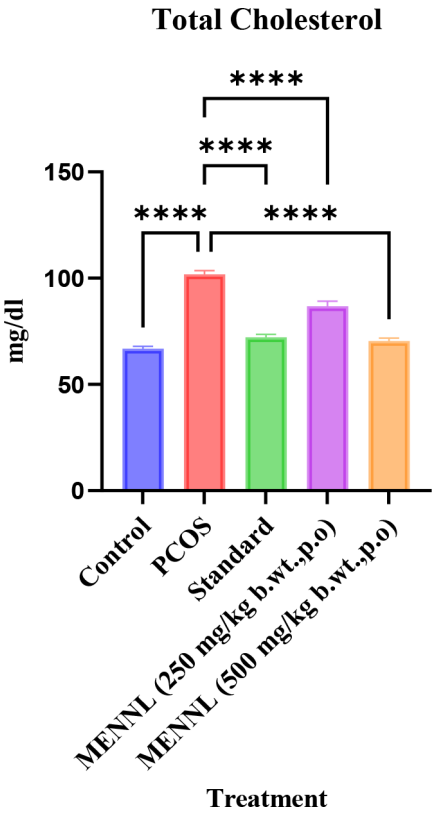
When compared to the control group, the PCOS rats' serum total cholesterol levels were considerably higher (P<0.001). Serum total cholesterol levels were significantly lower in rats treated with MENN at a dose of 250 mg/kg than in the PCOS group (P<0.05). Rats given 500 mg/kg of MENN showed a substantial reduction in total cholesterol levels when compared to the PCOS rats (P<0.001) (Figure 4).

3.5 Impact of MENN on Serum Triglyceride Levels of Rats

When compared to the control group, triglyceride levels were considerably higher (P<0.001) in PCOS rats. Triglyceride levels were significantly lower in rats treated with MENN at a dose of 250 mg/kg than in the PCOS rats (P<0.005). Rats given 500 mg/kg of MENN showed a substantial reduction in triglyceride levels when compared to the PCOS rats (P<0.001) (Figure 5).

3.6 Impact of MENN on Rats' Blood HDL-Cholesterol Levels

When compared to the control group, HDL-cholesterol levels were considerably lower (P<0.001) in PCOS rats.



Data represent mean ± SEM. ***P<0.001 versus control group, ***P<0.001 versus PCOS group (One-way ANOVA followed by Tukey's Post hoc test).

Figure 4. Effect of MENN on serum cholesterol levels.

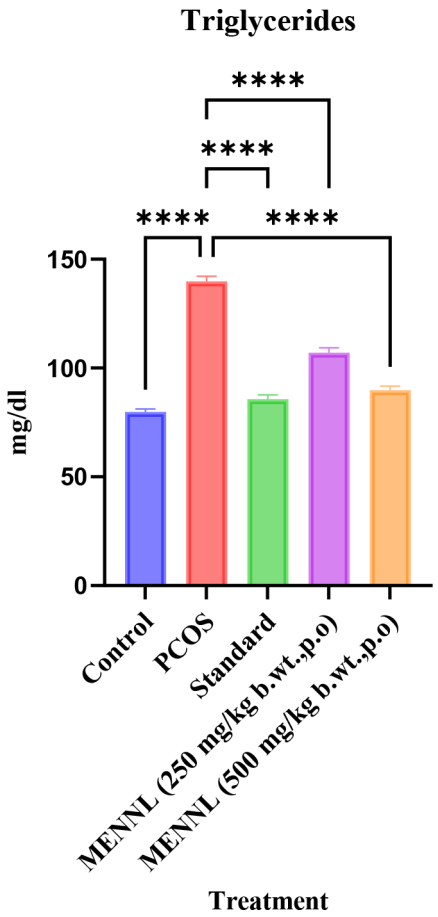
Rats administered 250 mg/kg of MENN demonstrated a substantial increase in HDL cholesterol levels as compared to the PCOS rats (P<0.05). Rats treated with MENN at a dose of 500 mg/kg had significantly higher HDL-cholesterol levels than the PCOS rats (P<0.001) (Figure 6).

3.7 Impact of MENN on Rats' Blood LDL-Cholesterol Levels

The PCOS rats' LDL-cholesterol readings were substantially higher than those of the control group (P<0.001). Rats given 250 mg/kg of MENN demonstrated a substantial reduction in LDL cholesterol levels as compared to the PCOS rats (P<0.05). Rats receiving 500 mg/kg of MENN had significantly lower LDL-cholesterol levels than the PCOS rats (P<0.001) (Figure 7).

3.8 Impact of MENN on Rats' Blood VLDL-Cholesterol Levels

When compared to the control group, VLDL cholesterol levels were considerably higher in PCOS



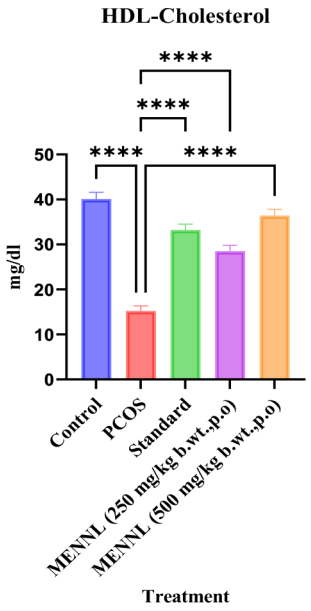
Data represent mean ± SEM. ***P<0.001 versus control group, ***P<0.001 versus PCOS group (One-way ANOVA followed by Tukey's Post hoc test).

Figure 5. Effect of MENN on serum triglyceride levels.

rats (P<0.001). When MENN received 250 mg/kg, their VLDL cholesterol levels significantly decreased when compared to the PCOS rats (P<0.05). The levels of VLDL cholesterol were considerably reduced. Rats treated with MENN received 500 mg/kg, which was significantly lower than that of the PCOS rats (P<0.001) (Figure 8).

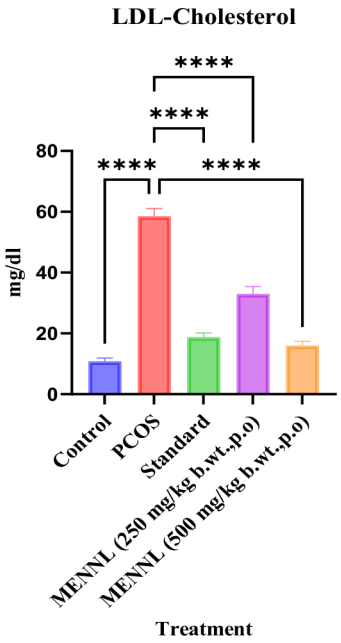
3.9 Impact of MENN on Superoxide Dismutase

When compared to the control group, the PCOS rats' ovarian SOD levels were considerably lower (P<0.001). When MENN received 250 mg/kg, their SOD levels significantly increased in comparison to the PCOS rats (P<0.05). In comparison to the PCOS rats, SOD levels were considerably restored in the high-dose group (500 mg/kg) (P<0.001) (Figure 9).



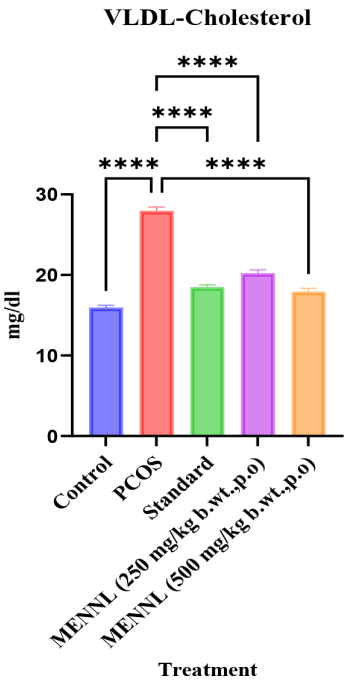
Data represent mean ± SEM. ***P<0.001 versus control group, ***P<0.001 versus PCOS group (One-way ANOVA followed by Tukey's Post hoc test).

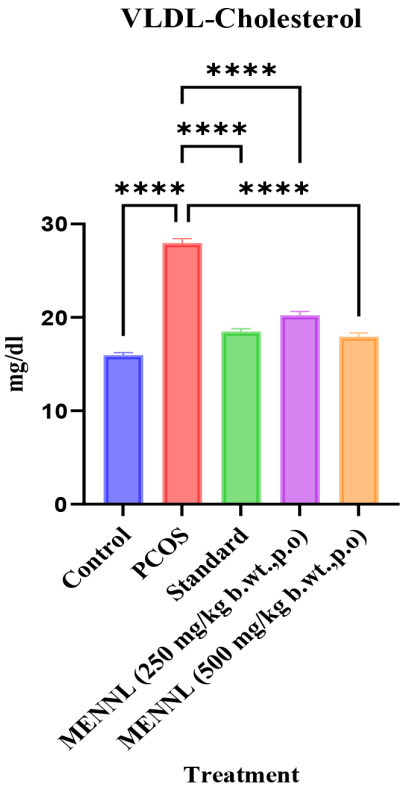
Figure 6. Effect of MENN on serum HDL - Cholesterol levels.



Data represent mean ± SEM. ***P<0.001 versus control group, ***P<0.001 versus PCOS group (One-way ANOVA followed by Tukey's Post hoc test).

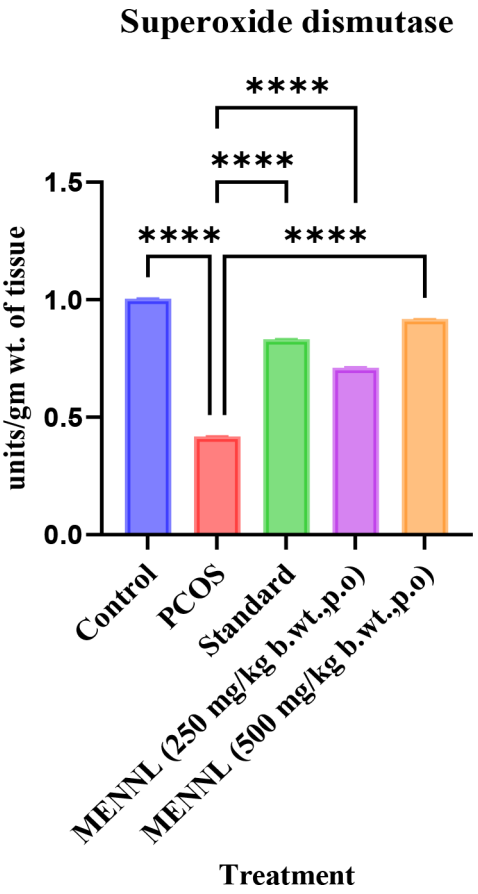
Figure 7. Effect of MENN on serum LDL cholesterol levels.





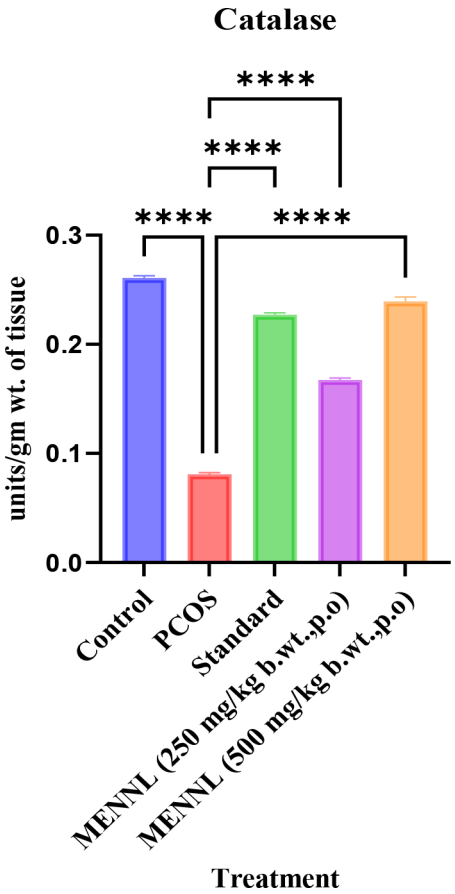
Data represent mean ± SEM. ***P<0.001 versus control group, ***P<0.001 versus PCOS group (One-way ANOVA followed by Tukey's Post hoc test).

Figure 8. Representing two images for the same parameter (VLDL - Cholesterol). Please remove any one duplicate image and keep title as Effect of MENN on serum VLDL - cholesterol levels.



Data represent mean ± SEM. ***P<0.001 versus control group, ***P<0.001 versus PCOS group (One-way ANOVA followed by Tukey's Post hoc test).

Figure 9. Effect of MENN ovarain superoxide dismutase.



Data represent mean ± SEM. ***P<0.001 versus control group, ***P<0.001 versus PCOS group (One-way ANOVA followed by Tukey's Post hoc test).

Figure 10. Effect of MENN ovarian catalase.

3.10 Impact of MENN on Catalase

When compared to the control group, the PCOS rats' ovarian catalase levels were considerably lower (P<0.001). When MENN received 250 mg/kg, their catalase levels significantly increased in comparison to the PCOS rats (P<0.05). In comparison to the PCOS group, the high-dose group (500 mg/kg) showed a considerable restoration of catalase levels (P<0.001) (Figure 10).

3.11 Impact of MENN on Reduced Glutathione

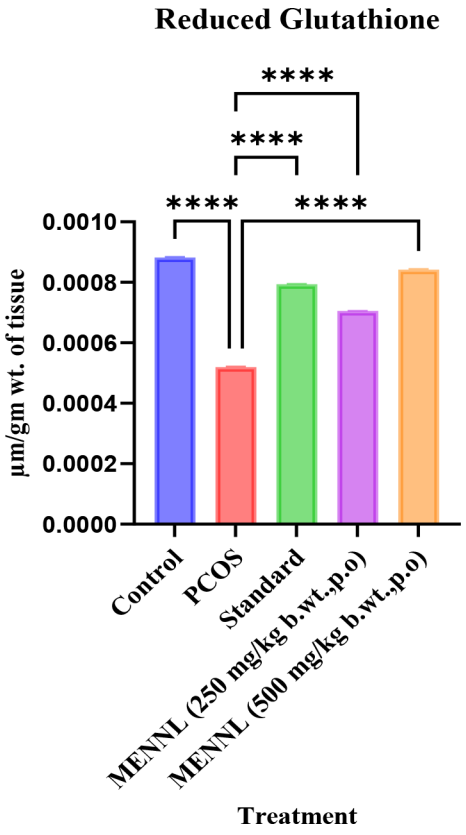
When compared to the control group, the PCOS rats' ovarian reduced glutathione levels were considerably lower (P<0.001). When MENN received 250 mg/kg, their decreased glutathione levels significantly increased (P<0.05) in comparison to the PCOS rats. In comparison to the PCOS rats, the high-dose group (500 mg/kg) showed a considerable restoration of reduced glutathione levels (P<0.001) (Figure 11).

3.12 Impact of MENN on Malondialdehyde

When compared to the control group, the PCOS rats' ovarian malondialdehyde levels were considerably higher (P<0.001). When MENN received 250 mg/kg, their malondialdehyde levels were decreased as compared to the PCOS rats (P<0.05). The high-dose group's malondialdehyde levels were considerably lower than those of the PCOS rats (P<0.001) (Figure 12).

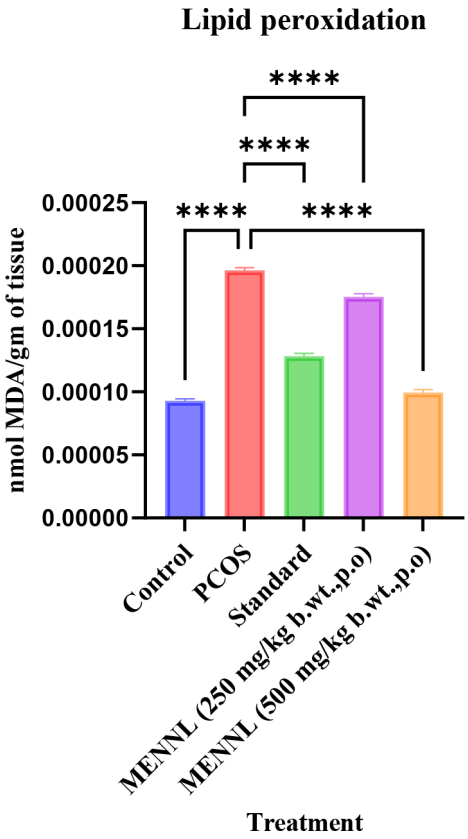
3.13 Ovarian Histopathology

Rats in the normal, PCOS, and therapy groups showed histological alterations in their ovaries. (A). The ovaries of the rats in the control group did not alter



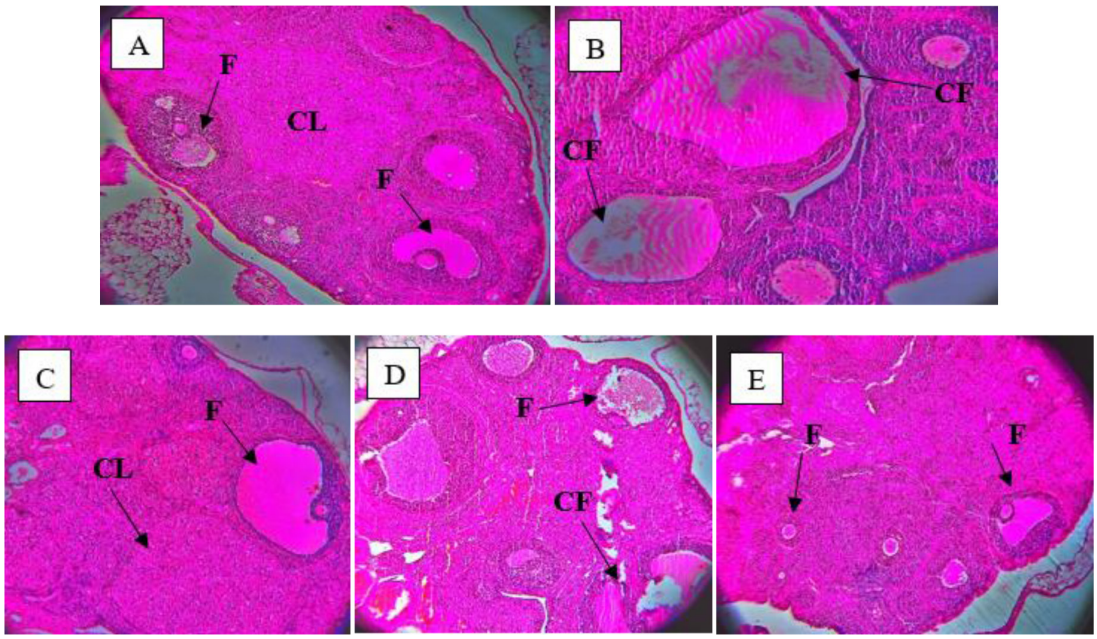
Data represent mean ± SEM. ***P<0.001 versus control group, ***P<0.001 versus PCOS group (One-way ANOVA followed by Tukey's Post hoc test).

Figure 11. Effect of MENN on ovarian reduced glutathione.



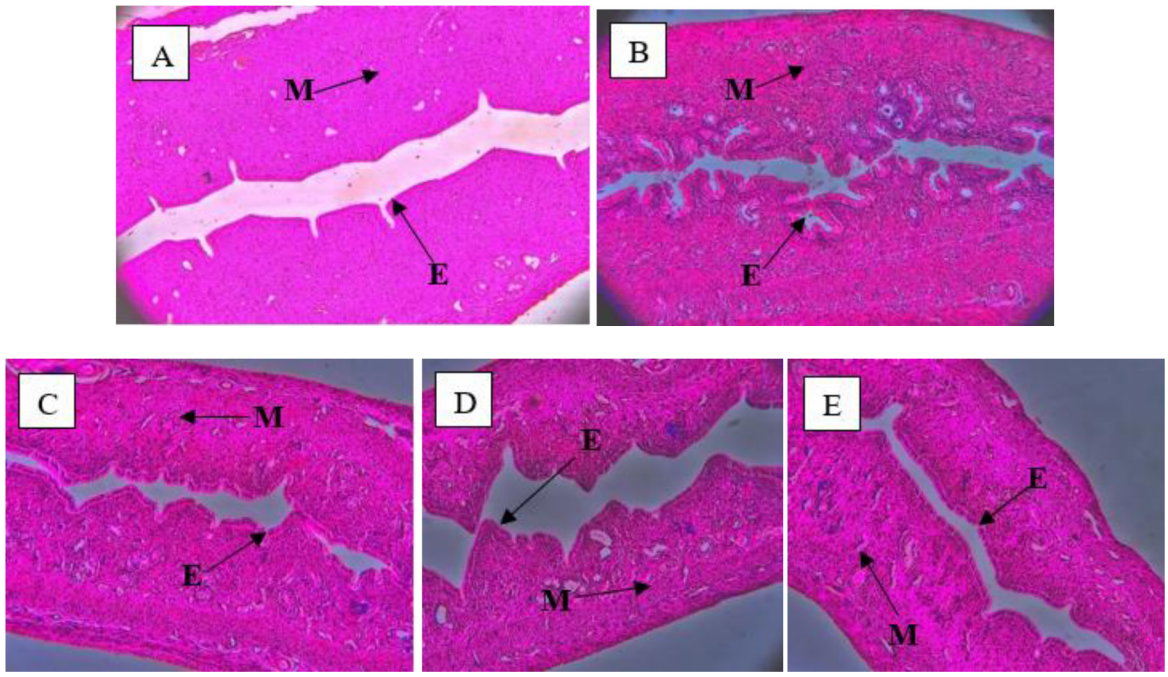
Data represent mean ± SEM. ***P<0.001 versus control group, ***P<0.001 versus PCOS group (One-way ANOVA followed by Tukey's Post hoc test).

Figure 12. Effect of MENN on lipid peroxidation.



F: Follicle, CF: Cystic follicle, and CL: *Corpus luteum*.

Figure 13. Histopathology of ovaries.



Note: Endometrium, and M: Myometrium.

Figure 14. Histopathology of the uterus.

morphologically. (B). PCOS rats' ovaries displayed a decrease in healthy follicles, an increase in different-sized cystic follicles, and no corpus luteum. (C). Rats given metformin had more healthy follicles, fewer cystic follicles, and more corpora lutea in the ovarian cortex. (D). Rats given 250 mg/kg of MENN revealed a small number of smaller cysts and a small corpus luteum. (E). Rats given 500 mg/kg of MENN exhibited healthy follicles and a corpus luteum of normal size, as well as the lack of cystic follicles, indicating that the animal had returned to its normal cyclic condition (Figure 13).

3.14 Uterine Histopathology

Rats in the normal, PCOS, and therapy groups showed histological alterations in their uteruses. (A). The uterus of the rats in the control group did not alter morphologically. (B). The uterus of PCOS rats had endometrial hyperplasia, which was manifested by irregular folds of endometrial cells into the uterus lumen, formation of adenomyosis in the endometrium, and a marked decrease in uterus length and epithelial cell height. (C). The uterus's length and epithelial cell height significantly increased after taking metformin; endometrial thickness decreased, and adenomyosis, which is indicative of normal uterine morphology, appeared. (D). Rats administered 250 mg/kg of MENN exhibited moderate adenomyosis and endometrial hyperplasia, as evidenced by short endometrial folds into the lumen of the uterus. (E). Rats given 500 mg/kg of MENN had normal uterine morphology, indicating less adenomyosis and endometrial hyperplasia (Figure 14).

4. Discussion

Women of reproductive age are frequently affected by PCOS, a common endocrine condition that has a major effect on fertility and pregnancy outcomes[11]. By controlling the menstrual cycle (oral contraception), lowering blood testosterone levels (glucocorticoids), improving IR (metformin), and promoting ovulation (clomiphene), some of the negative symptoms of PCOS can be lessened[12]. Interest in safer, plant-based options has increased due to the drawbacks of traditional PCOS therapies, including the increased risks during pregnancy[13]. *Nelumbo nucifera* Gaertn (Lotus) is a member of the *Nelumbonaceae* family[14,15] that grows on the water's flood surface. The current study aims to assess the methanolic extract of *Nelumbo nucifera* against Letrozole-induced polycystic ovary syndrome in female rats. The weight of adult female rats with PCOS was significantly higher than that of the NC

group. Rats given MENN at doses of 250 mg/kg and 500 mg/kg had a dose-dependent, significant reduction in body weight as compared to the PCOS group, and the outcomes were in line with earlier research. Additionally, PCOS is closely associated with type 2 diabetes and hyperglycemia, both of which contribute to the development of insulin resistance[16]. Rats with PCOS had significantly higher serum glucose levels than rats without the condition. When MENN was administered to PCOS rats at doses of 250 mg/kg and 500 mg/kg, the rats' serum glucose levels significantly decreased in comparison to the PCOS group. It may be achieved through enhancing insulin production, enhancing insulin-mediated glucose absorption, and inhibiting intestinal absorption of excess glucose. These results corroborate the previous study, which found that plant extracts that have a positive impact on PCOS also lower hyperglycemia[17]. Total testosterone levels in PCOS rats[18] are used to assess hyperandrogenemia, another key aspect of PCOS. In this study, we also used letrozole to upset the equilibrium between the releases of different hormones. Letrozole inhibited aromatase activity[19], which in turn enhanced testosterone synthesis. In our investigation, we also discovered that rats with PCOS had much higher testosterone levels than rats without the condition. Serum testosterone levels in PCOS rats treated with MENN at doses of 250 mg/kg and 500 mg/kg significantly decreased in a dose-dependent manner as compared to the PCOS group. In PCOS, hyperandrogenism and hyperinsulinemia cause adipocytes to lipolyze, which raises free fatty acids and causes dyslipidemia[20]. In comparison to normal rats, PCOS-induced animals in this study exhibited a considerable drop in HDL cholesterol and a significant increase in serum total cholesterol, triglycerides, LDL, and VLDL cholesterol. When MENN was administered to PCOS rats at doses of 250 mg/kg and 500 mg/kg, the blood lipid profile significantly returned to normal. *N. nucifera's* strong hypoglycemic and anti-androgenic qualities may be the cause. Oxidative stress is brought on by an excess of ROS and may be a factor in many illnesses that impact female reproduction[21]. Oxidative stress and cell damage are caused by lipid peroxidation and aberrant ROS generation. The most widely used marker for lipid peroxidation assessment, which reflects OS, is malondialdehyde; higher ROS causes higher MDA levels[22]. Compared to normal rats, the PCOS rats' ovarian tissue exhibited a large increase in MDA levels and a significant drop in SOD, CAT, and GSH. In comparison to PCOS rats, PCOS animals treated with MENN at doses of 250 mg/kg and 500 mg/kg exhibited a decrease in MDA levels in ovarian tissue and a significant increase in SOD, CAT, and GSH. These findings align with previously published data that showed similar outcomes. Significant histological changes were seen in the uterus and ovarian tissue of rats with PCOS. The normal histoarchitecture of the ovaries and uterus was restored in PCOS rats treated with 500 mg/kg of MENN.

5. Conclusion

Our study's findings imply that *N. nucifera* methanolic extract possesses antihyperglycemic, testosterone-lowering, lipid-lowering, and antioxidant properties. It has also been shown to ameliorate the histological characteristics of ovarian and uterine tissue in rats with PCOS. To find the active pharmaceuticals among the many phytoconstituents found in *N. nucifera*'s methanolic extract, additional research on fractions from partial purification of the extract is necessary. We think that the extract of *N. nucifera* may help treat PCOS in women because these studies have revealed a possible treatment for the condition.

6. Acknowledgement

Our heartfelt thanks to the management of Raghavendra Institute of Pharmaceutical Education and Research for supporting the lab facilities to carry out the research work.

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Author Contribution

Ideation and Conceptualisation, K.S.R.; methodology P.S.S and S.G.; Statistical analysis and software, G.S and S.G.; writing - original draft preparation, K.S.R.; writing - review and editing, K.S.R. and B.K.S.; supervision, K.S.R. and A.S. All authors have read and agreed to the published version of the manuscript.