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# Effects of *Plantago Major* on Serum Lipid Profile and Histopathological Changes of Ovaries in Induced Polycystic Ovary Syndrome in Female Rats

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## Abstract

**Background** About 4-8% of women of reproductive age have polycystic ovary syndrome (PCOS), also known as Stein-Leventhal syndrome. PCOS is a heterogeneous endocrine condition.

**Objective** To investigate the impact of *Plantago major* (*P. major*) leaves extract on the lipid profile and histological picture of the ovary in female rats with induced PCOS, and to contrast the impact of *P. major* leaves extract with that of Metformin.

**Methods** Female rats were divided into six groups: apparent healthy group, PCOS induction group, Metformin-treated group, high-dose *P. major* group (1500 mg/kg/day), low-dose Plantago major group (1000 mg/kg/day), and a combination group treated with *P. major* (500 mg/kg/day) and Metformin. The measured parameters included serum lipid profile {total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein cholesterol (VLDL-C)} and histopathological evaluation of ovarian tissue.

**Results** Except for HDL-C, which was significantly increased compared to the induction group, the lipid profile parameters were significantly reduced in the *P. major* treated groups. Ovarian histology revealed recovery of ovulation in rats treated with Plantago major.

**Conclusion** In comparison to Metformin, Plantago major treatment groups showed better effects in terms of easing PCOS symptoms in female rats.

**Keywords** Plantago major, leaves, polycystic ovary syndrome, female rats, lipid profile.

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**List of abbreviations:** HDL-C = High-density lipoprotein cholesterol, LDL-C = Low-density lipoprotein cholesterol, P. major = Plantago major, PCOS = Polycystic ovary syndrome, TC = Total cholesterol, TG = Triglycerides, VLDL-C = Very low-density lipoprotein cholesterol

## Introduction

A diverse endocrine conditions known as polycystic ovary syndrome (PCOS), also known as Stein-Leventhal syndrome, affects around 4-8% of women of reproductive age [(1)]. PCOS symptoms include hirsutism (clinical hyperandrogenism), biological hyperandrogenemia (high levels of androgen in the blood), ovulatory arrest (menstrual dysfunction), thicker ovarian stroma, polycystic ovarian morphology on ultrasound, and infertility. Metabolic issues like diabetes (increased insulin resistance) and obesity are

usually linked to PCOS [2]. Lifestyle modifications are one non-pharmacological PCOS therapy strategy [3]. People with high body mass index who want to lose weight may benefit from taking weight-reducing medication, such as Orlistat [4].

The first-line treatment for ovulation induction is Clomiphene citrate. Hormonal irregularities, acne, and hirsutism have all been treated with a combination contraceptive that contains both estrogen and progestin [5]. Spironolactone, Flutamide, and Cyproterone acetate are examples of antiandrogens that are first-line therapies for hirsutism because they inhibit androgen receptors to lower androgen output [6].

Some hyperandrogenic symptoms are treated by insulin sensitizing medications like Metformin and Troglitazone by reducing total and free testosterone levels. It encourages ovulation, lessens the effects of insulin resistance, and controls excessively high testosterone levels. The menstrual cycle, ovulation, and fertility are all helped to return [7].

Since ancient times, people have looked for medicines in nature to cure dreadful diseases. Erythromycin, Clarithromycin, Amoxycillin, and Amphotericin B are natural product-derived antibiotics and antifungal drugs. Paclitaxel, Docetaxel, and Campothecin are natural product-derived anticancer and cholesterol-lowering treatments [8].

The Plantaginaceae family's *Plantago major* (*P. major*), also referred to as large plantain, is frequently used in medicine [9]. A few of the known effects of *P. major* are anti-hypercholesteremia, anti-atherosclerosis, hypoglycemic impact, antinociceptive, antioxidant, and free radical scavenging. antibiotic, anti-malarial, anti-viral, anti-fungal, anti-obesity, and anti-giardiasis [10].

In the current study, female rats with PCOS caused by Letrozole are treated with a methanolic extract of Plantago major leaves, To investigate the impact of *P. major* leaves extract on the lipid profile and histological picture of the ovary in female rats with induced PCOS, and to contrast the impact of *P. major* leaves extract with that of Metformin.

## Methods

### Plant collection and authentication

The plant's leaves were taken in June 2021 from an area North of Baghdad, Iraq. The botanist at the College of Science, University of Diyala, Prof. Dr. Khazzal Al-Jubouri, recognized and verified it.

### Preparation of plant extract

The plant material's leaves were cleaned, air dried at room temperature in the shade, ground electrically, and weighed. The dried, defatted material was extracted using a Soxhlet equipment. Soxhlet's spherical flask was filled with 450 ml of 80% methanol. The substance was removed for around 12 hr or until it was fully depleted. The alcoholic extract was filtered via filter paper to get rid of the marc. Using a rotary evaporator and reduced pressure, the filtrate was concentrated to around 15 ml before being mixed with 50 ml of distilled water for leaf extraction. Leaf extracts were subjected to chemical tests to conduct a preliminary qualitative phytochemical investigation, and the amount of phenolic and flavonoid components is assessed by high-performance thin layer chromatography (HTLC) analysis [11].

### High performance thin layer chromatography

Using the traditional method, a preliminary qualitative phytochemical analysis of *P. major* extract was performed to identify phytoconstituents like flavonoids, glycosides, steroids, phenols, and terpenoids [12].

### A. Test for cardiac glycosides

In 2 ml of glacial acetic acid that also contained one drop of 1% ferric chloride, 0.5 ml of the extract was dissolved ($FeCl_3$). This solution had 1 ml of sulfuric acid underneath it ($H_2SO_4$). At the interface, a brown ring developed that revealed the presence of deoxy-sugar.

**B. Test for steroids**

After being dissolved in 3 mL of chloroform ($CHCl_3$), 0.5 ml of the sample extract was filtered. To create a lower layer, a few drops of concentrated ($H_2SO_4$) were added to the filter. The presence of steroids was confirmed by the appearance of a reddish-brown ring.

**C. Test for flavonoids**

Ten ml of the leaf extract aqueous filtrate were treated with 0.5 ml of diluted ammonia ($NH_4OH$) solution and 0.5 ml of conc. ($H_2SO_4$). The appearance of a yellow tint indicated the presence of flavonoids. Normally, the yellow tint disappears when you stand.

**D. Test for saponins**

The best assay for detecting saponins was used, the foaming test. In a test tube, 0.5 ml of the sample extract was mixed with 5 ml of distilled water. The existence of saponons was determined by the solution's stable, enduring froth after being vigorously agitated.

**E. Test for tannins**

Before filtering, 0.5 ml of the extract was heated in 10 ml of distilled water. The presence of tannins was demonstrated by brownish green or blue-black coloring after a few drops of 1% $FeCl_3$ were applied.

**F. Test for alkaloids**

- Meyer's test: A boiling water bath was used to dissolve 0.5 ml of sample extract in 5 ml of 1% hydrochloric acid (HCl), then the mixture was filtered. To 1 ml of filtrate, a few drops of Meyer's reagent were added. White precipitate or turbidity were indicators of the presence of alkaloids.
- Dry extract precipitate test: 4 ml of methanol, 400 ml of glacial acetic acid, and a few drops of ammonia were added to 0.5 gm of dry sample extract in order to conduct this test ($NH_4OH$). Alkaloids were present in the precipitate, which was evident.

**G. Test for terpenoids**

Terpenoids in the extract were discovered using the Salkowski test. After being treated with 2 ml of $CHCl_3$, 3 ml of conc, 0.5 gram of the sample extract was used ($H_2SO_4$). The presence of terpenoids near the contact was confirmed by a reddish-brown tint.

**Experimental Design**

***Animal grouping***

In order to conduct the study, sixty female albino rats weighing 180-200 g at 4 weeks of age were selected. They were procured from the animal house of the Baghdad University of Pharmacy and housed at Al-Nahrain University. Each of the ten animals was kept in a standard metal cage, which had a maintenance temperature of about (22.8±0.7) °C, a humidity of about (41.6±6.6%), and a diurnal change of about 12 hours of light and dark. Fresh water and chow food were provided to the animals, and the air in the room was continuously changed by means of a ventilating vacuum (ad libitum). Before we began operating on them, it was crucial that they acclimate to the animal home environment for at least a week [13].

***Study design***

Six groups of sixty albino female rats were randomly selected, and all appeared to be in fair health:

- Apparent healthy group: Ten female rats had normal feeding for 51 days.
- Induction group: Ten female rats received Letrozole (5.3 mg/kg) orally for 21 days to induce PCOS, followed by 30 days of regular feeding.
- Ten female rats from the Metformin group received oral Metformin (500 mg/kg) for 30 days after undergoing PCOS for 21 days.
- Large dosage *P. major* group: After induced PCOS for 21 days, 10 female rats received oral doses of *P. major* (1500 mg/kg) for 30 days.
- Minimal dose Plantago major group: After induced PCOS for 21 days, 10 female rats

received oral doses of *P. major* (1000 mg/kg) for 30 days.

- Combination group: 10 female rats received oral doses of 500 mg/kg of *P. major* and 250 mg/kg of metformin for 30 days after inducing PCOS for 21 days.

**PCOS induction in rats**

Orally given doses of Letrozole (5.3 mg/kg/day for 21 days) totaling 0.4 ml were used for the induction. A vaginal swab was collected and examined daily at 9:00 am until a persistent diestrus phase was noticed in order to allow PCOS induction [14].

**Measurement of Serum Lipid Profile**

- **Serum total cholesterol (TC) determination**: Serum TC was calculated using Richmond's method [15].

- **Serum triglyceride (TG) determination**: Serum TG levels were calculated using the Fossati and Principe method [16].

- **Serum high, low and very low-density lipoprotein cholesterol (HDL-C, LDL-C and VLDL-C) determinations**: Serum HDL-C levels were calculated using Burstein's method [17].

For these aims, a pre-made kit called the Rat Cholesterol and Triglyceride ELISA Kit by Linear/Spain has been employed.

**Histopathological study**

The animal was dissected after being given chloroform anesthesia in a glass container, and the ovaries were carefully extracted from the oviduct using a delicate surgical scissor and forceps. in the subsequent recovery of the ovaries on a petri dish and removal of fatty tissue [18]. At the conclusion of the induction period and the conclusion of the treatment period.

**Statistical analysis**

Data analysis was carried out using statistical package for social sciences (SPSS) software (version 23). Data illustrated as mean±standard deviation (SD) in addition to median and range. According to data normality of distribution by Shapiro Wilk test, unpaired ttest and ANOVA tests used for normally distributed data, whereas Mann Whitney U test and Kruskal Wallis test for data that were not normally distributed. P value less than 0.05 was considered the level of significance.

## Results

**Phytochemical screening test**

For the purpose of qualitative chemical identification of phytoconstituents, a dried powdered extract of *P. major* leaves was subjected to a preliminary phytochemical screening test. The test showed that steroids contained phenols, flavonoids, terpenoids, and glycosides, as stated in table (1).

**Table 1. Phytochemical screening of Plantago major leaves extract**

| No. | Phytoconstituents | *Plantago major* |
|---|---|---|
| 1 | Phenols | ++ |
| 2 | Flavonoids | + |
| 3 | Alkaloids | - |
| 4 | Terpenoids | * |
| 5 | Saponins | - |
| 6 | Steroids | ++ |
| 7 | Glycosides | + |

+: present, ++: present in bulk, *: present in less amount; -: absent

**Effects of *P. major* on serum lipid profile**

With the exception of HDL-C, where it was considerably lower than that of the apparent healthy group (P <0.05), the levels of lipid profile were significantly higher among the induction group in comparison to the apparent healthy group, as shown in table (2).

**Table 2. Comparison between apparent healthy group and induction group regarding lipid profile**

| Parameter | | Groups | | P value |
|---|---|---|---|---|
| | | Healthy | Induction | |
| LDL-C (mg/dl) | Mean±SD | 18.88±5.59 | 64.33±11.52 | <0.001* |
| | Median (Range) | 17.74 (13.28-25.63) | 63.37 (53.9-85.3) | |
| VLDL-C (mg/dl) | Mean±SD | 5.56±1.17 | 13.43±2.31 | 0.002** |
| | Median (Range) | 6.17 (3.91-6.51) | 14.8 (10.32-15.2) | |
| HDL-C (mg/dl) | Mean±SD | 7.05±2.01 | 4.01±0.43 | 0.041** |
| | Median (Range) | 7.85 (3.72-9.12) | 4 (3.5-4.79) | |
| TC (mg/dl) | Mean±SD | 31.49±4.17 | 81.77±12.04 | <0.001* |
| | Median (Range) | 30.15 (27.8-37.72) | 77.44 (72.7-104.2) | |
| TG (mg/dl) | Mean±SD | 27.79±5.87 | 67.15±11.55 | 0.002** |
| | Median (Range) | 30.84 (19.55-32.54) | 74.02 (51.62-76.02) | |

LDL-C: Low density lipoprotein-cholesterol, VLDL-C: Very low-density lipoprotein-cholesterol, HDL-C: High density lipoprotein-cholesterol, TC: Total cholesterol, TG: Total triglyceride. *Unpaired ttes, **Mann-Whitney U test

Comparing the levels of lipid profile between the *P. major* treated groups and the induction group showed that they were considerably lower in the *P. major* treated groups than in the induction group (P <0.05).

When LDL-C, VLDL-C, TC, and TG levels were compared between the Metformin-treated group and the *P. major*-treated group, it was found that the LDL-C, VLDL-C, and TC levels were significantly lower in the *P. major*-treated group than in the Metformin-treated group, while the HDL-C levels were significantly higher. In comparison to other groups, the high dose *P. major* treated group's lipid profile was much lower as shown in table (3).

**Table 3. Comparison between Metformin treated group and *Plantago major* treated groups (high dose, low dose, and in combination with Metformin) regarding lipid profile**

| Parameter | | Groups | | | | P value |
|---|---|---|---|---|---|---|
| | | Metformin | High dose *P. major* | Low dose *P. major* | *P. major* & Metformin | |
| LDL-C (mg/dl) | Mean±SD | 36.77±7.48 | 13.05±3.24 | 25.94±4.65 | 20.28±4.63 | <0.001* |
| | Median (Range) | 36.31 (26.58-46.29) | 13.48 (7.25-17.23) | 26.59 (18.69-30.78) | 20.72 (11.67-24.72) | |
| VLDL-C (mg/dl) | Mean±SD | 10.61±0.67 | 4.8±0.36 | 5.19±0.27 | 5.16±0.27 | 0.001** |
| | Median (Range) | 10.59 (9.79-11.52) | 4.87 (4.2-5.16) | 5.29 (4.86-5.47) | 5.16 (4.7-5.49) | |
| HDL-C (mg/dl) | Mean±SD | 2.28±1.04 | 5.0±1.41 | 2.83±0.98 | 3±0.89 | 0.021** |
| | Median (Range) | 2.34 (0.85-3.51) | 5 (3-7) | 2.5 (2-4) | 3 (2-4) | |
| TC (mg/dl) | Mean±SD | 49.66±7.75 | 22.86±3.38 | 33.98±4.21 | 28.43±4.95 | <0.001* |
| | Median (Range) | 48.94 (39.58-60.98) | 23.32 (17.17-26.43) | 33.7 (27.93-39.25) | 28.61 (20.01-34.21) | |
| TG (mg/dl) | Mean±SD | 53.04±3.36 | 24.03±1.82 | 25.97±1.33 | 25.78±1.35 | 0.001** |
| | Median (Range) | 52.98 (48.97-57.62) | 24.33 (21.01-25.8) | 26.48 (24.28-27.35) | 25.82 (23.5-27.44) | |

LDL-C: Low density lipoprotein-cholesterol, VLDL-C: Very low-density lipoprotein-cholesterol, HDL-C: High density lipoprotein-cholesterol, TC: Total cholesterol, TG: Total triglyceride. *ANOVA test, **Kruskal Wallis test

**Effects of P. major on histopathological study**

The number of corpus luteum, was significantly lower in the induction group compared to the group that appeared to be in good health, opposite to number of cystic follicles, which were significantly higher in induction group (P <0.05). Whereas the thickness of theca layer, thickness of granulosa layer, and number of graafian follicles were lower in induction group than healthy group but not reached the significant level. The number of atretic follicles were insignificantly higher in induction group than in healthy group P = 0.485 as depicted in table (4) and figure (1).

**Table 4. Comparison between apparent healthy group and induction group regarding histopathological picture of ovary**

| Parameter | | Groups | | P value* |
|---|---|---|---|---|
| | | Healthy | Induction | |
| Thickness of theca layer (µm) | Mean±SD | 17.24±13.54 | 0±0 | 0.065 |
| | Median (Range) | 23.6 (0-28.63) | 0 (0-0) | |
| Thickness of granulosa layer (µm) | Mean±SD | 24.45±18.99 | 0±0 | 0.065 |
| | Median (Range) | 35.13 (0-38.77) | 0 (0-0) | |
| No. of corpus luteum | Mean±SD | 4±0.89 | 1.67±0.82 | 0.004 |
| | Median (Range) | 4 (3-5) | 1.5 (1-3) | |
| No. of cystic follicles | Mean±SD | 1.33±0.82 | 5.17±2.14 | 0.002 |
| | Median (Range) | 1.5 (0-2) | 5 (3-8) | |
| No. of atretic follicles | Mean±SD | 1.5±1.05 | 2.17±1.6 | 0.485 |
| | Median (Range) | 1.5 (0-3) | 2 (0-4) | |
| No. of graafian follicles | Mean±SD | 0.67±0.52 | 0±0 | 0.065 |
| | Median (Range) | 1 (0-1) | 0 (0-0) | |

*Mann-Whitney U test

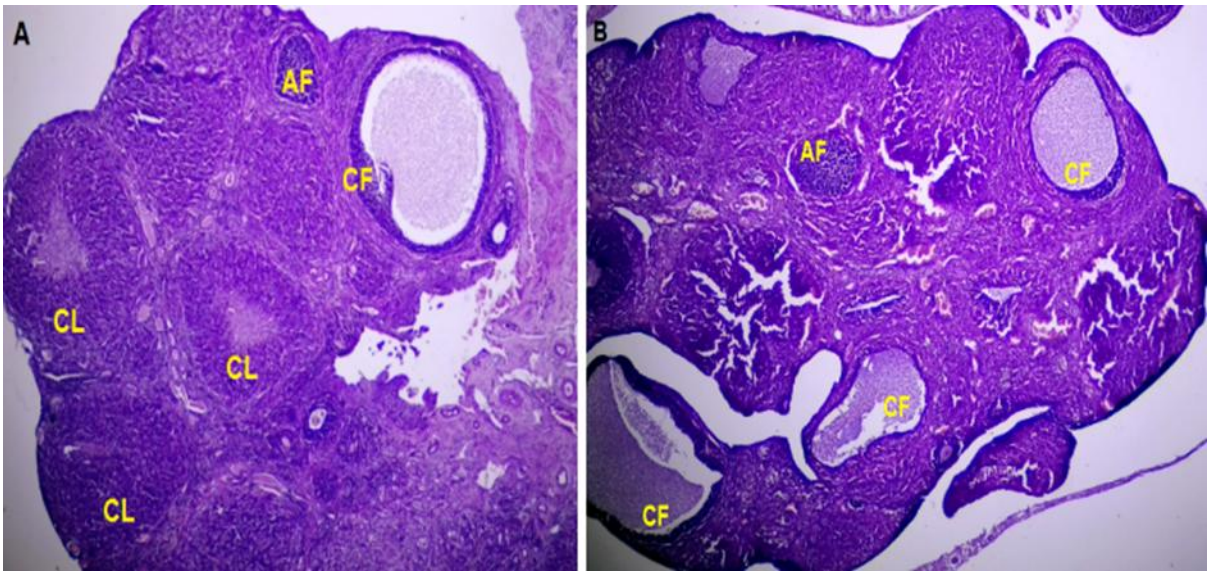


**Figure 1. Ovarian indices of rats. (A) Ovary of apparent healthy group, (B) Ovary of induction group, in which CF: cystic follicles, CL: corpus luteum, AF: atretic follicles**

In comparison to the induction group, the number of corpus luteum and graafian follicles was significantly higher in the *P. major* treated groups, whereas the number of cystic follicles was significantly lower in the *P. major* treated groups, P <0.05. When comparing the high dose *P. major* treated group to the metformin treated group, the thickness of the granulosa layer was dramatically enhanced, while the number of cystic follicles was significantly decreased, P <0.05.

Compared to the metformin-treated group, the low dosage *P. major* treatment group had considerably less cystic follicles, P <0.05. Plantago major and metformin treated groups had considerably higher granulosa layer thickness than metformin treated groups, P<0.05. When compared to other groups, the high dose Plantago major treated group had much thicker theca and granulosa layers and more atretic follicles, P <0.05 as shown in table (5) and figure (2).

**Table 5. Comparison between Metformin treated group and Plantago major treated groups (high dose, low dose, and in combination with Metformin) regarding histopathological picture of ovary**

| Parameter | | Groups | | | | P value* |
|---|---|---|---|---|---|---|
| | | Metformin | High dose *P. major* | Low dose *P. major* | *P. major* & Metformin | |
| Thickness of theca layer (µm) | Mean±SD | 15.41±12.67 | 26.1±1.31 | 11.62±12.79 | 25.4±2.01 | 0.018 |
| | Median (Range) | 19.77 (0-31.23) | 26.64 (24.01-27.53) | 10.83 (0-25.5) | 24.68 (23.27-28.35) | |
| Thickness of granulosa layer (µm) | Mean±SD | 28.39±22.05 | 56.69±6.33 | 24.82±27.51 | 53.22±2.38 | 0.004 |
| | Median (Range) | 41.09 (0-45) | 55.04 (50.28-65.26) | 22.67 (0-57.25) | 52.89 (50.39-56.93) | |
| No. of corpus luteum | Mean±SD | 3.17±1.47 | 4.5±0.84 | 3.67±1.21 | 3.67±1.21 | 0.389 |
| | Median (Range) | 3.5 (1-5) | 4 (4-6) | 3.5 (2-5) | 3.5 (2-5) | |
| No. of cystic follicles | Mean±SD | 2.0±0.63 | 0.5±0.55 | 0.5±0.55 | 2.67±1.03 | 0.001 |
| | Median (Range) | 2 (1-3) | 0.5 (0-1) | 0.5 (0-1) | 3 (1-4) | |
| No. of atretic follicles | Mean±SD | 1.67±0.82 | 2.33±1.03 | 1.0±0.89 | 1.0±0.0 | 0.036 |
| | Median (Range) | 1.5 (1-3) | 2 (1-4) | 1 (0-2) | 1 (1-1) | |
| No. of graafian follicles | Mean±SD | 0.67±0.52 | 2.0±1.55 | 0.83±1.17 | 1.5±0.84 | 0.080 |
| | Median (Range) | 1 (0-1) | 1.5 (1-5) | 0.5 (0-3) | 1 (1-3) | |

*Kruskal-Walli's test where p significant at < 0.05 and high significant at <0.001

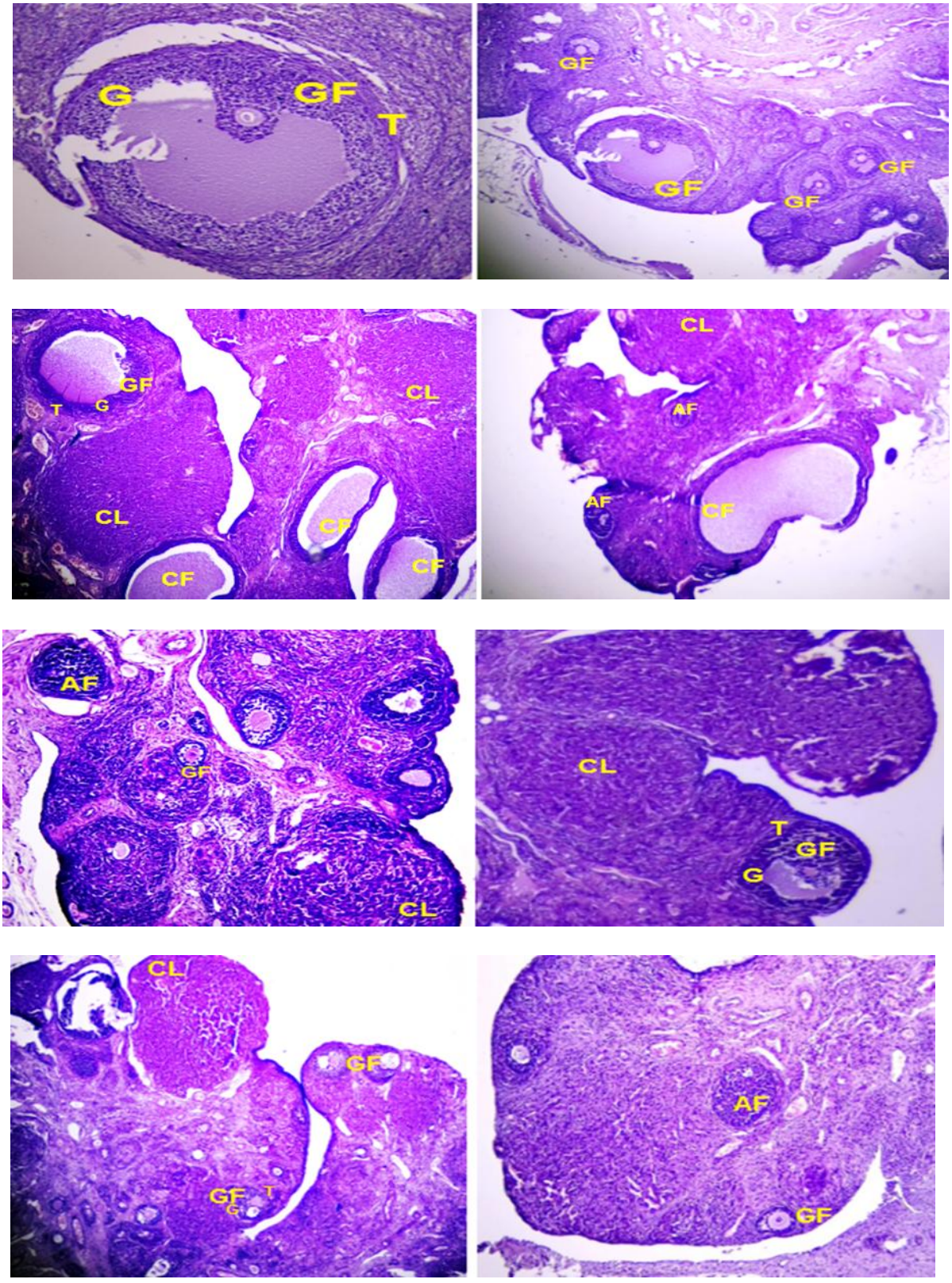


**Figure 2. Ovarian indices of rats; (A) Ovary of Metformin treated group (B) Ovary of high dose Plantago major treated group, (C) Ovary of low dose Plantago major treated group (D) Ovary of combination of Plantago major with Metformin treated group, in which CF: cystic follicles, CL: corpus luteum, AF: atretic follicles, GF: graffian follicles, G: thickness of granulosa layer and T: thickness of theca layer**

## Discussion

PCOS is an ovarian disorder that disrupts the reproductive axis and results in a number of metabolic and hormonal symptoms. According to the cause of the malfunction, PCOS is classified (hyperandrogenemia, anovulation and polycystic ovarian morphology) [19].

Because insulin resistance can lead to dyslipidemia, the induction group in the current study had considerably higher cholesterol levels than the group that appeared to be in good health [20]. When comparing the induction PCOS group to the apparently healthy group, other lipid profile markers, such as LDL-C and VLDL-C, show a significant increase. This is most likely due to an excessive hypersecretion of apo-lipoprotein B and VLDL-C from the liver in response to insulin stimulation, which causes hypertriglyceridemia [21]. Due to increased HDL catabolism during puberty, letrozole decreased HDL levels [22].

In comparison to other treated groups, the high dose *P. major* treated group had significantly lower LDL-C, VLDL-C, cholesterol, and triglyceride levels while having significantly higher HDL-C levels. This could be because the high dose *P. major* treated group contained a higher concentration of active ingredients (apigenin, rutin, catechin, and quercetin) than other treated groups. Due to the presence of quercetin, the plant extract's potential to lower LDL levels may be attributed to an increase in LDL receptors [23,24].

These lipid profiles may be interpreted as ovarian parameter histological alterations. According to Jahan et al., quercetin treatment causes ovarian tissue to mend significantly with the development of graafian follicles, a considerable decrease in cysts, and regular luteinization [25]. Greater corpus luteum in the groups treated with *P. major* suggested that the estrous cycle had been restored to normal operation.

In conclusion, in female rats, a *P. major* leaf extract showed relief in PCOS symptoms. LDL-C, VLDL-C, cholesterol, and triglyceride levels in serum were dramatically reduced by *P. major* leaf extract, whilst HDL-C levels were significantly increased. Additionally, the extract from *P. major* leaves reduced the number of atretic and cystic follicles while increasing the amount of corpus luteum and graafian follicles, which helped to restore ovulation. In comparison to Metformin, *P. major* treatment groups saw better effects in terms of easing PCOS symptoms in female rats. Additionally, the high dose *P. major* treated group saw improved outcomes as compared to the other treated groups, which shows significant promise for potential clinical uses in the future.

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## Author contribution

Al-Jawadi: Performed the experimental work, data collection, statistical analysis, and manuscript preparation. Dr. Gatea: Supervised the study, interpreted the results. Both authors approved the final version of the manuscript.

## Conflict of interest

The authors declare no conflict of interest.

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