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Role of *Plantago major* on biochemical and reproductive hormons in experimental induced PCOS in female rats

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ABSTRACT

About 4-8% of women of reproductive age suffer from polycystic ovary syndrome (PCOS), also known as Stein-Leventhal syndrome, a diverse endocrine condition. Research the impact of *Plantago major* leaves extract on the induced polycystic ovarian syndrome in rats, assess the impact of *Plantago major* leaves extract on biochemical markers (Adiponectin and serum blood glucose), and examine the impact of *Plantago major* leaves extract on hormones (FSH, LH, testosterone, and estrogen), and contrast the impact of *Plantago major* leaves extract with that of metformin. Female rats were treated for 21 days with 0.4 mL of oral letrozole (5.3 mg/kg) before receiving a dose of Metformin (500 mg/kg) for the first group, a high dose of *Plantagomajor* (1500 mg/kg) for the second group, a low dose of *Plantagomajor* (1000 mg/kg), and a combination of *Plantagomajor* (500 mg/kg) and metformin (250 mg/kg) for the third group. Compared to the induction group, the *plantagomajor* treated group had reduced levels of glucose, testosterone, and LH, but higher levels of adiponectin, estradiol, and FSH. In comparison to metformin, *plantago major* treatment groups saw greater effects in terms of easing PCOS symptoms in female rats.

1. Introduction

About 4-8% of women of reproductive age have polycystic ovarian syndrome (PCOS), also known as Stein-Leventhal syndrome, an endocrine condition with heterogeneous symptoms [1]. PCOS symptoms include hirsutism, thicker ovarian stroma, polycystic ovarian morphology on ultrasound, ovulatory arrest (menstrual dysfunction), biological hyperandrogenemia (higher androgen levels in the blood), and infertility. Metabolic issues including diabetes (increased insulin resistance) and obesity are usually linked to PCOS [2]. Options for non-pharmacological PCOS treatment include modifying one's lifestyle [3]. People with high BWI who want to lose weight may benefit from taking weight-reducing medications, such as orlistat [4]. The first-line treatment for ovulation induction is clomiphene citrate. Hormonal contraceptives that contain both estrogen and progesterone have been used to treat hirsutism, acne, and

irregular menstrual cycles [5]. Spironolactone, flutamide, and cyproterone acetate are examples of antiandrogens that are recognized as first-line therapy for hirsutism since they inhibit androgen receptors to decrease androgen secretion [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 restored [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]. *Plantago major* (*P. major*), often known as large plantain, is a member of the Plantaginaceae family and is frequently used as medicine [9]. Anti-hypercholesteremia, anti-atherosclerosis, hypoglycemic impact, antinociceptive, antioxidant, and free radical scavenging are just a few of the actions that *plantago major* is known to have. anti-obesity, anti-giardiasis, anti-fungal, anti-viral, anti-malarial, and antibiotic [10].

The current study examines the effectiveness of treating female rats with PCOS caused by letrozole with a methanolic extract of *Plantago major* leaves.

2. Materials and Method

2.1 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.

2.2 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 hours 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 are subjected to chemical tests to conduct a preliminary qualitative phytochemical investigation, and high-performance liquid chromatography analysis is utilized to quantify the amount of phenolic and flavonoid components [11].

2.3 High performance thin layer chromatography (HPTLC)

To find phytoconstituents such flavanoids, glycosides, steroids, phenols, and terpenoids, a preliminary qualitative phytochemical investigation of *Plantago major* extract was carried out using the conventional approach [12]. The phenols and flavonoids in the leaf extract of *Plantago major* were studied. Under ideal circumstances, the main chemical was separated on an FLC (Fast Liquid Chromatographic) column [13].

2.4 Experimental Design

2.4.1 Animal grouping

At the age of four weeks, sixty female albino rats were selected for the study and were procured from the animal house of the Baghdad University of Pharmacy before being housed at Al-Nahrain University. The animals were albino and appeared to be in good health. Each of the ten animals was kept in a standard metal cage with fresh water and chow food. The room's air was continuously changed by a ventilating vacuum, and the animals were maintained at a maintenance environmental temperature of about (22.8 0.7) ^{o}C, a humidity level of (41.6 6.6) percent, and a diurnal change of about 12 h light/dark (ad libitum). Before we

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began working on them, it was crucial that they acclimate to the environment of the animal house for at least a week [14].

2.4.2 Study design

Six groups of sixty albino female rats, all of which appeared to be in good health, were chosen at random:

- Apparent healthy group: For 51 days, ten female rats got regular nutrition.
- Induction group: Letrozole (5.3 mg/kg) was given orally to ten female rats to induce PCOS for 21 days, followed by 30 days of regular feeding.
- The Metformin group consisted of ten female rats that had been given PCOS for 21 days before receiving oral Metformin (500 mg/kg) for 30 days.
- High dosage *Plantago major* group: 10 female rats were given oral doses of *Plantago major* (1500 mg/kg) for 30 days after being given PCOS for 21 days.
- Low dosage *Plantago major* group: 10 female rats were given oral doses of *Plantago major* (1000 mg/kg) for 30 days after being given PCOS for 21 days.
- Combination group: 10 female rats were given PCOS for 21 days, after which they received oral doses of 500 mg/kg of *Plantago major* and 250 mg/kg of metformin for 30 days.

2.5 PCOS induction in rats

Letrozole (5.3 mg/kg) in 0.4 mL daily doses for 21 days were supplied orally during the induction. A vaginal swab was collected and examined daily at 9:00 am until a persistent diestrous phase was noticed in order to allow PCOS induction [15].

2.6 Blood sample preparation

An overnight fasting rat was given ether anesthesia in a glass jar, followed by the collection of 6 mL of blood from a heart puncture with a 3cc syringe and transfer of the blood into a gel tube. The samples were then allowed to clot for an additional hour at room temperature. The serum was then spun at 3,000 RPM for 10 minutes to separate it.

2.7 Measurement of serum blood glucose

Serum blood glucose levels are measured using the enzymatic calorimetry technique [16].

2.8 Principle of the assay for adiponectin and hormonal measurement

This assay employs a competitive enzyme immunoassay methodology. This kit comes with a rat ELISA kit for Adiponectin, Testosterone, Estradiol, FSH, and LH from My Biosource in the USA.

2.9 Statistical Analysis

Data analysis was carried out using SPSS statistical software (version 23). Simple descriptive statistics were used for data analysis, including the mean standard error (SE), t-test, ANOVA, and post-hoc analysis. A 0.05 p value indicates a statistically significant level.

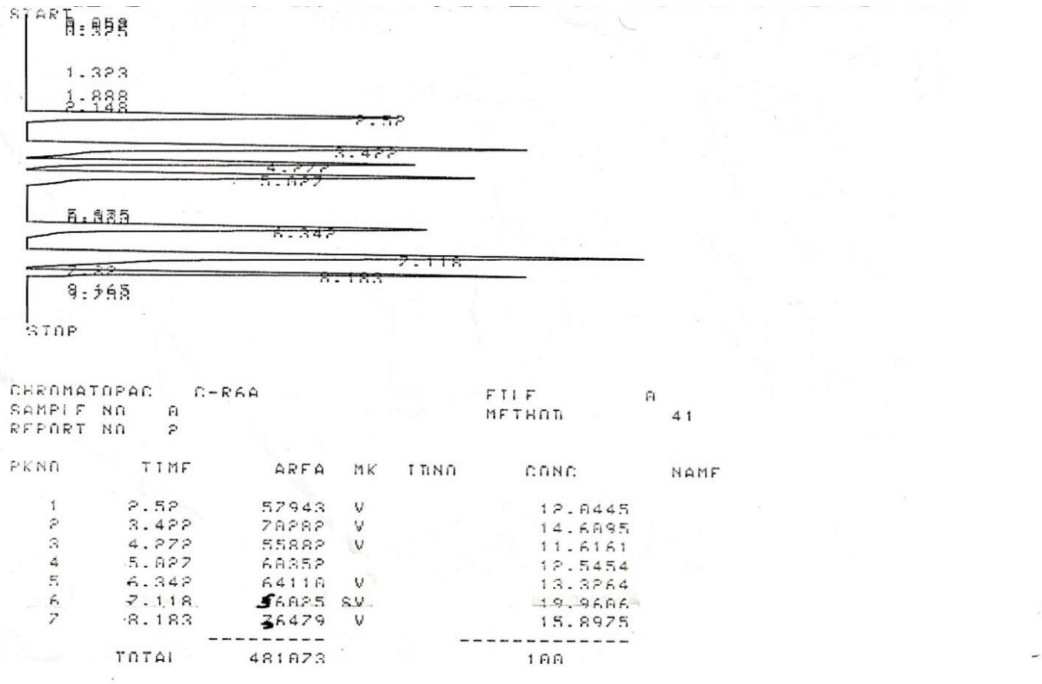
3. Results

3.1 High performance thin layer chromatography (HPTLC)

According to the standard, the HPTLC examination showed the presence of 7 different phenols and flavonoids compounds; the spots are produced and detected at 335 nmas under UV illumination (1-2).

The extract's HPTLC chromatography displays seven peaks at various Rf values, with peak number 2

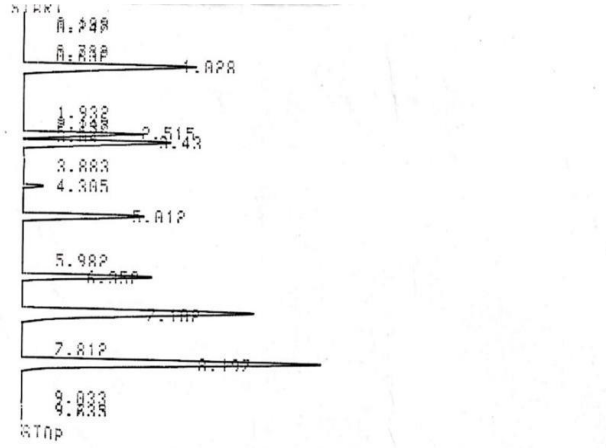
having a well-defined Rf value of 3.10 and a percent area of approximately21.53% of the extract contents as shown in Table 1.



CHROMATOPAC C-R6A FILE A
SAMPLE NO A METHOD 41
REPORT NO 2

PKNO	TIME	AREA	MK	TANO	CONC	NAME
1	2.52	57943	V		12.8445	
2	3.422	70282	V		14.6895	
3	4.272	55882	V		11.6161	
4	5.827	60352			12.5454	
5	6.342	64110	V		13.3264	
6	7.118	86825	SV		19.9666	
7	8.183	76479	V		15.8975	
	TOTAL	481073			100	

Figure 1: HPTLC chromatography of standard phenols and flavonoids.



CHROMATOPAC C-R6A FILE A
SAMPLE NO A METHOD 41
REPORT NO 3

PKNO	TIME	AREA	MK	TANO	CONC	NAME
1	1.828	38516	V		10.7868	
2	2.515	35564	SV		9.96	
3	3.43	38846	S		10.8794	
4	4.385	21839	V		6.1162	
5	5.812	31798			8.9312	
6	6.352	48226	V		13.5064	
7	7.182	69116	SV		19.3569	
8	8.197	73066	V		20.463	
	TOTAL	357863			100	

Figure 2: HPTLC chromatography of phenols and flavonoids components of *Plantago major* leaves

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extract.

Table 1: HPTLC screening of *Plantago major*leaves extract

No.	Subjects	Retention timeR_f	Area uv	Conc.25 µg/ml each	Area %
1	Gallic acid	2.52	57943	767.2	13.6
2	Catechin	3.42	70282	690.9	12.3
3	Caffeic acid	4.27	55882	488.5	8.7
4	Luteolin	5.02	60352	660.5	11.7
5	Rutin	6.34	64110	940.3	16.7
6	Apigenin	7.11	96925	891.4	15.8
7	Quercetin	8.18	76479	1194.2	21.2

3.2 Effects of Plantago major on biochemical markers (glucose and adiponectin)

When compared to the apparent healthy (A.H.) group, the induction group's glucose was considerably higher ($P<0.05$). Comparing high dosage *Plantago major* treated groups to induction group and other treatment groups, high dose *Plantago major* treated groups exhibit considerably lower levels of glucose.

Adiponectin levels in the induction group were substantially lower than in the group of people who appeared to be in good health, and in the high dose *Plantago major* treated group, they were significantly greater than in the induction group and other groups $P< 0.05$, as indicated in the tables (2-3).

3.3 Effects of Plantago major onhormones

Compared to the apparent healthy group, the levels of the hormones (testosterone and LH) were significantly higher in the induction group, with the exception of estradiol and FSH, where they were significantly lower ($P<0.05$). The levels of hormones (testosterone and LH) in each group treated with high, low, or a combination of high and low doses of *plantago major* and metformin are significantly lower than in the induction group, with the exception of estradiol and FSH, which were significantly elevated following treatment with high and low doses of *plantago major* in comparison to the induction group, as shown in the tables (2-3).

4. Discussion

PCOS is an ovarian disorder that disrupts the reproductive axis and results in a variety of metabolic and hormonal symptoms [17]. According to the cause of the malfunction, PCOS is classified (hyperandrogenemia, anovulation and polycystic ovarian morphology) [18].

Since there is no specific drug to treat PCOS syndrome and only a few medications are licensed for the condition's most common symptoms, people must utilize off-label medications including Metformin, Statins, Thiazolidinediones, and Spironolactone to manage their symptoms [19].

Although, there is insufficient evidence to support the effectiveness and safety of complementary and alternative therapies, like acupuncture and herbal therapy, many studies have suggested that they may help

with PCOS symptoms. Therefore, novel therapeutic methods including complementary and alternative medicines must be researched in order to maximize PCOS therapy [20].

The effect of *Plantago major* leaf extract on rats with PCOS caused by letrozole has been investigated in the current study. Herbal supplements are used therapeutically for PCOS therapy while contrasting hormonal and metabolic alterations to conventional medicine (Metformin). Thus, it was helpful for the current investigation to investigate its therapeutic potential on the PCOS rat model.

With the exception of (Adiponectin, Estradiol, and FSH), where they were significantly lower than those among the apparent healthy group, $P<0.05$, the levels of biochemical markers and hormones were significantly higher among the induction group in the current study when compared with the apparent healthy group.

Oral use of *Plantago major* in high dosages dramatically lowers elevated lipid and blood sugar profiles, In order to achieve its hypolipidemic effects, *Plantago major* extract inhibits the production of fatty acids, speeds up fatty acid -oxidation, and stimulates cholesterol catabolism, mostly through phenylpropanoid glycosides [20]. *Plantago major* protects CAT, CA, MDA, and GSH from lipid peroxidation and oxidative stress. By boosting antioxidant status and reducing lipid peroxidations, *Plantago major* exerts its chemopreventive actions [21].

The phytochemical analysis of *Plantago major* leaf extract in the current study revealed the presence of flavonoids and phenols, which may be the cause of *Plantago major's* ability to normalize blood glucose levels. For instance, quercetin promotes glucose absorption by activating AMPK-dependent and insulin-independent pathways to increase the amount of the glucose transporter 4 (GLUT-4). Additionally, it blocks essential gluconeogenesis-related enzymes and preserves the islet -cell activity [22]. It was discovered that rutin lowers blood sugar levels and boosts insulin-dependent receptor kinase activity [23], Catechin inhibits the enzyme known as catechol-O-methyltransferase (COMT), which is in charge of breaking down norepinephrine. Norepinephrine's protracted effects on lipid metabolism [24], According to reports, the polyphenolic substance catechin found in leaves inhibits -glucosidase and -amylase activities, lowering blood sugar levels [25],

The serine-threonine protein kinase Akt2 kinase, also known as protein kinase B, is thought to be affected by luteolin in order to increase insulin sensitivity. Because Akt2 stops the insulin receptor from losing its phosphorylation, the insulin signaling mechanism isn't diminished. The translocation of the glucose transporter GLUT4 to the cell's surface mediates the effect of Akt2, which is also in charge of controlling glucose absorption. The following methods explain how apigenin reduces insulin resistance and abnormalities of glycolipid metabolism. It prevents the insulin receptor kinase domain's tyrosine nitration, which reduces insulin resistance. Apigenin lessens -amylase's inhibition, which slows down the breakdown of dietary carbs [26].

The presence of substances like terpenoids, steroid, and glycosides (such as iriodid glycoside). (iridoid glycoside) has an anti-diabetic effect by inhibiting glucose-6-phosphatase (G6Pase) and glycogen phosphorylase-a (GPa). Inhibiting GPa was thought to be a potential target for treating diabetes because it promotes glycogen synthesis while also acting as a physiologic regulator of hepatic glycogen metabolism [27]. By examining the glucose uptake in cells, the steroid (-sitosterol) demonstrated a significant inhibition on - amylase and - glucosidase activity, the antidiabetic activity, and it also prevents the high-fructose diet-induced hypertriglyceridemia, visceral obesity, and hypoadiponectinemia. It also improves glycemic control

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and reduces insulin resistance through the regulation of [28].

The acceleration of fatty acid -oxidation, along with the suppression of fatty acid synthase in adipose tissue and the activation of lipolysis, are additional anti-obesity actions of *Plantago major* [29].

Using a phytochemical screening test and an HPTLC approach, the current study was able to link the activity of *Plantago major* on hormonal levels to flavonoid, phenol, steroid, and glycoside elements identified in the plant's leaves.

The presence of the aforementioned phytosterols may be a factor in the modulation of steroidogensis. Studies have shown that β-sitosterol, which has an estrogen-like effect and regulates steroidogensis by structurally resembling cholesterol, can affect endogenous hormones by altering bile acid metabolism and estrogen absorption or by competing with cholesterol as a substrate for the synthesis of steroids and hormones [30].

On the other hand, phytoestrogens have a high affinity for binding to the estrogen receptor (β) and are comparable to estradiol in terms of their estrogenic capabilities for alleviating menopausal symptoms [31]. Phytosterols in particular has the capacity to block 5αR activity due to their structural similarities to the current 5α-Rs inhibitors [32]. Flavonoids may encourage proliferation because some of them have estrogenic characteristics and others have ER- binding affinities [33].

According to a study by Hong Y et al., quercetin reduces the activity of the steroidogenic enzymes 3 -HSD and/or 17 -HSD type 7 (important for androgen synthesis) in rat models with PCOS, with no effect on 17 -HSD type 1 (which plays a role in estrogen synthesis), which in turn regulates androgen levels. According to studies, quercetin effectively raises serum levels of testosterone and LH by reducing resistance, which boosts androgen production in a variety of ways [34]. Because oxidative stress is linked to other conditions such as insulin resistance, ovarian mesenchyme hyperplasia, and infertility, quercetin's anti-oxidative stress characteristics were established by preventing that by upregulating antioxidant enzyme [35].

According to certain research, a phenomena in which lower plasma androgen is brought on by a decrease in ovarian androgen production by insulin may be analogous to a decline in plasma levels of LH in response to the reducing in insulin. Quercetin showed anti-androgenic activities via inhibiting the PI3K (Phosphatidylinostirol-3 Kinase) pathway and down-regulating the CYP17A1 gene. While metformin did not significantly downregulate the CYP17A1 gene, this suggests that it may affect ovarian steroidogenesis by modifying insulin levels [22].

The current statistical analysis for each group shows a significant decrease in LH level and a considerable increase in FSH level when using *Plantago major* groups in comparison to the induction group. Each group of *Plantago major* regulates the FSH/LH ratio to its normal level.

There is little research on the role of *plantago major* in the treatment of PCOS for sex hormones (LH, FSH, testosterone, and estrogen). To the best of our knowledge, the study that examines the effects of *Plantago major* on PCOS rats is the one that has the alterations indicated above.

Table 2: Comparison between apparent healthy group and induction group regarding hormones and biochemical markers

Parameter	Groups	P value

	Apparent healthy group		Induction group		
	Mean	**SD**	**Mean**	**SD**	
Glucose(mg/dl)	70.45	12.61	158.79	31.05	<0.001
Adiponectin(µg/ml)	11.89	3.76	2.27	0.39	<0.001
Testosterone(ng/ml)	3.29	1.91	32.50	8.06	<0.001
Estradiol(ng/ml)	39.60	3.22	23.40	1.95	<0.001
LH(mIU/ml)	27.05	1.60	43.14	2.59	<0.001
FSH(ng/ml)	139.79	17.83	23.47	2.48	<0.001
LH: Luteinizing hormone, FSH: Follicle stimulating hormone.					

Table 3: Comparison between metformin treated group and *Plantago major* treated groups (high dose, low dose, and in combination with metformin) regarding hormones and biochemical markers.

Parameter	**Groups**								**P value**
	Metformin treated group		**High dose *Plantago major* treated group**		**Low dose *Plantago major* treated group**		***Plantago major* & metformin treated group**		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Glucose(mg/dl)	74.49	8.75	69.00	13.96	65.01	4.53	70.14	14.94	0.56
Adiponectin(µg/ml)	4.90	2.07	6.58	3.09	5.39	1.82	8.91	3.39	0.07
Testosterone(ng/ml)	3.79	2.09	3.97	2.33	4.63	2.41	3.26	.15	0.69
Estradiol(ng/ml)	33.21	4.44	35.28	3.70	35.21	3.05	32.72	2.71	0.51
LH(mIU/ml)	17.06	6.67	24.94	1.33	25.18	3.85	24.68	3.79	0.01
FSH(ng/ml)	68.26	20.08	55.54	14.64	34.60	4.27	108.32	42.84	0.001
LH: Luteinizing hormone, FSH: Follicle stimulating hormone.									

5. Conclusion

In female rats, a *plantago major* leaf extract showed relief in PCOS symptoms. Adiponectin levels were dramatically raised while blood glucose levels were significantly reduced by *plantago major* leaf extract. Additionally, *Plantago major* leaf extract dramatically elevated FSH and estrogen hormonal levels while considerably decreasing LH and testosterone hormonal levels that affect rat ovulation. In comparison to metformin, *plantago major* treatment groups saw greater effects in terms of easing PCOS symptoms in female rats. Additionally, the high dose *Plantago major* treated group saw improved outcomes when compared to other treated groups, which shows significant promise for potential clinical uses in the future.

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