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Comparative Evaluation of *Piper Longum* and *Ipomoea Batata* in Restoration of Ovarian Function in Letrozole Induced PCOS in Rats with Respect to Clomiphene Citrate.

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ABSTRACT:
Polycystic ovary syndrome (PCOS) is a common endocrine-metabolic disorder characterized by hyperandrogenism, anovulation, insulin resistance, and polycystic ovarian morphology. The present study aimed to evaluate the comparative effect of *Ipomoea batata* and *Piper longum* on ovarian function in letrozole-induced PCOS rats with respect to clomiphene citrate. PCOS was induced in female Wistar rats using letrozole (1 mg/kg, p.o.) for 28 days. Following induction, animals received clomiphene citrate, *Ipomoea batata* (100 and 200 mg/kg), or combinations of *Ipomoea batata* and *Piper longum* for 35 days. Letrozole administration produced hyperglycemia, dyslipidemia, hormonal imbalance, increased ovarian weight, disrupted estrous cyclicity, and cystic ovarian changes. Treatment with *Ipomoea batata* significantly improved these abnormalities in a dose-dependent manner. The combination therapy produced greater therapeutic effects, with the IB2 + PL group showing marked restoration of estrous cyclicity, normalization of hormonal and biochemical parameters, reduction in ovarian weight, and recovery of normal ovarian architecture. The findings suggest that combined administration of *Ipomoea batata* and *Piper longum* may serve as a promising herbal therapeutic strategy for PCOS management.

1. INTRODUCTION:
Polycystic ovary syndrome (PCOS) is one of the most frequently diagnosed endocrine disorders among women in their reproductive years, affecting approximately 2–7% of this population. It is typically characterized by menstrual disturbances and elevated androgen levels, often occurring alongside metabolic abnormalities such as insulin resistance and compensatory hyperinsulinemia [1]. PCOS is strongly associated with reproductive complications, including infertility, irregular uterine bleeding, recurrent pregnancy loss, and adverse pregnancy outcomes [2]. A hallmark endocrine feature of the condition is disrupted gonadotropin regulation, particularly increased luteinizing hormone (LH) secretion and an altered LH to follicle-stimulating hormone (FSH) ratio [3].

Beyond reproductive dysfunction, PCOS is closely linked to metabolic comorbidities such as dyslipidemia, hypertension, endothelial dysfunction, and impaired glucose metabolism. A significant proportion of affected women exhibit abnormal lipid profiles, and obesity is common within this subgroup. These lipid abnormalities contribute to the development of atherosclerosis, thereby elevating long-term cardiovascular risk [2,4]. Insulin resistance and dyslipidemia frequently coexist in PCOS, promoting hyperglycemia and its related complications [3]. Excess insulin levels further aggravate the disorder by stimulating ovarian androgen production, lowering circulating sex hormone–binding globulin concentrations, and disrupting normal ovulatory processes [5].

Management strategies often involve combined pharmacological therapy, including insulin-sensitizing agents such as metformin and thiazolidinediones, along with lipid-lowering drugs like statins, nicotinic acid, and fibrates [6,7,8]. However, long-term administration of these medications has been associated with notable adverse effects [9]. Therefore, there is growing interest in identifying safer and more effective alternative therapeutic approaches for the management of PCOS.

Piper longum Linn., Piperaceae, is growing in warmer regions of India, Western Ghats, Central Himalaya to Assam and Bengal as a small aromatic plant. Leaves are smooth, entire, 7-ribed, narrow pointed, sessile, 6–10 cm long, deeply cordate with big lobes at the base, dark green and shining, stalked. Flowers are dioecious, minute, inflorescence a spike, 3–4 cm long. Roots contain parenchyma, simple or compound starch grains, lignified and striated stone cells and pith is absent. Fruits are small, ovoid, sunken in fleshy spike, 2.5–4 cm long, blackish green and shining. Fruits mainly contain sesamin, sylvatine, a lignan dihydrostimasterol, piperine, N-isobutyl-decatrans-2-trans-4-dienamide, terpinolene, zingiberone, p-cymene, p-methoxyacetophenone, dehydrocarveol and phenylethyl alcohol. The leaves contain hentriacontane, triacontanol and β-sitosterol [11].

Piper longum Linn. Has been found to show activities such as insulin resistance contributing to anovulation, hyperandrogenism and cardiovascular risks [12,13]. It is also known to possess action against Parkinson's disease [14], obesity [15], glioma [16], hyperlipidemia [17], diabetes [18], hormone-induced melanoma [19] and neuronal damage [20].

Ipomoea batatas (L.) Lam., commonly known as sweet potato, belongs to the family Convolvulaceae and is a member of the genus Ipomoea, the largest genus within this family [21]. It is considered one of the most significant food crops globally and ranks among the major staple crops after rice, wheat, maize, and cassava in many developing countries [22]. Although the crop originated in tropical regions of Central and South America, it is presently cultivated extensively across tropical and subtropical regions, with major production reported in China, Malawi, Tanzania, Nigeria, and Indonesia [23].

Botanically, sweet potato is a tuberous-rooted perennial plant that is typically cultivated as an annual crop. The plant develops slender, creeping or trailing vines that may extend up to 4 m in length and contain milky latex. The leaves are generally ovate to cordate and borne on long petioles, showing variations in shape and color depending on the cultivar. The flowers are relatively uncommon and possess a funnel-shaped corolla that ranges from white to pale purple, while the fruit consists of round capsules containing flattened seeds [24]. Considerable diversity exists among sweet potato cultivars, particularly in the color of the tuber skin and flesh, including purple, yellow, and orange variations [25].

Sweet potato is also recognized for its rich phytochemical composition and nutritional value. Various plant parts, including the roots, tubers, leaves, and stems, contain numerous bioactive constituents such as polyphenols, flavonoids, anthocyanins, carotenoids, terpenoids, saponins, glycosides, alkaloids, steroids, and tannins [26-29]. Among these compounds, phenolic constituents including caffeic acid, chlorogenic acid, and various caffeoylquinic acid derivatives represent the predominant bioactive components. In addition, sweet potato serves as an important source of essential nutrients such as carbohydrates, dietary fiber, protein, vitamin C, β-carotene, and minerals [30,31].

Traditionally, sweet potato has been utilized in several countries, including Malaysia, Pakistan, the Philippines, Indonesia, and Tanzania, for both nutritional and medicinal purposes. It has been used as a dietary energy source and in the management of conditions such as anemia, allergies, and diabetes mellitus [32-37]. Furthermore, numerous studies have demonstrated that the bioactive constituents of sweet potato exhibit diverse pharmacological activities, including antioxidant, anti-inflammatory, antibacterial, anticancer, antihypertensive,

hypolipidemic, antidiabetic, hepatoprotective, wound healing, and immunostimulatory effects [38].
Low molecular weight *Piper longum* and *Ipomoea batata* which were used in the present study have already been evaluated for acute oral toxicity, subchronic toxicity and mutagenic potential [39]. Therefore, present study was carried out with an objective to evaluate comparative the effect of *Piper longum* and *Ipomoea batata* on letrozole-induced PCOS in adult female Wistar rats.

Clomiphene citrate is widely used in the management of polycystic ovary syndrome and functions as an ovulation-inducing agent while also influencing insulin sensitivity, similar to the action of metformin. It helps in lowering insulin resistance, which subsequently reduces ovarian androgen production and contributes to improved menstrual regularity [5,40]. Although conventional pharmacological treatments are effective, they are often associated with several adverse effects, including joint or muscle pain and musculoskeletal disturbances [9], lactic acidosis [41], and certain psychological disturbances such as mood changes and anxiety [42]. Because of these limitations, the development of safer therapeutic alternatives has become an important area of research. In this context, various herbal medicines have traditionally been used for the management and prevention of PCOS [42] However, despite their traditional use, many medicinal plants still require detailed investigation to better understand their pharmacological mechanisms and therapeutic potential [42].

MATERIALS AND METHODS

IAEC Approval

The protocol was approved by the Institutional Animal Ethics Committee (IAEC), CAYMET's Siddhant college of Pharmacy, Pune, Maharashtra, India (IAEC approval no. SCOP/IAEC/2025/10) constituted according to guidelines of Committee for the Purpose of Control and Supervision on Experiment on Animals.

Experimental Animals

Female Wistar rats with body weight ranging from 250-300 g and 8 weeks old were procured from the Institute's animal house and were maintained at a temperature of 25±1°C and relative humidity of 45 to 55% under 12-h light: 12-h dark cycle with free access to food pellets (Raviraj Enterprises, Rajgurunagar, India) and water ad libitum. All experiments were carried out between 09:00 and 17:00 h. These animals were randomly divided into seven groups (n = 6) as normal group, PCOS control group [LTZ 1 mg/kg/p.o], Standard group [CC, 100 mg/kg/p/o.,], *Ipopmoea batata* [100 mg/kg/p.o.] (IB1), *Ipomoea batata* [200 mg/kg/ p.o.] (IB 2), *Ipomoea batata* [100 mg/kg/p.o.] + *Piper longum* [200 mg.kg/p.o.] (IB 1 + PL), *Ipomoea batata* [200 mg/kg/p.o.] + *Piper longum* [200 mg.kg/p.o.] (IB 2 + PL)

Drugs and Chemicals

Letrozole (LETROZ TAB, Sun Pharma India, Ltd), Clomiphene citrate (SIPHENE-100, Serum Institute of India Pvt. Ltd., India), *Piper longum* and *Ipomoea batata* were obtained Mankarnika, chinchwad Pune. Other chemicals used in this study were of analytical grade. Glucose, Cholesterol, Triglycerides, HDL and Total protein kits were obtained from Erba analyzer, India (Total Protein System Pack)

Induction of PCOS and Sample Collection

All the animals except in normal group were orally administered with letrozole (1 mg/kg, p.o.) dissolved in 0.5 Carboxy Methyl Cellulose (CMC) once daily for 28 days (Kafali et al., 2004). Normal group received vehicle only (0.5% CMC). Vaginal smears were collected on daily basis and microscopic evaluation was carried out using Giemsa stain, that confirmed induction of PCOS. After 28 days treatment with letrozole, rats in all groups were administered with respective treatment from day 29 to day 63. After 28 days, PCOS control group and after 63 days, animals from other groups were kept on overnight fasting. Blood was collected by retro orbital puncture, serum was separated and used for estimation of hormones, glucose and lipid parameters. The animals were euthanized using CO_2 Chamber (inhalational) and sacrificed. Ovaries and uterus were excised, fat was cleaned off and weighed. After excision, ovaries were made blood- free, cleaned with ice cold saline and were used for further histopathological studies.

Estimation of Biochemical Parameters in Blood/Serum

Blood was centrifuged at 3000 rpm for 30 m; serum was separated and used for the estimation of blood glucose, total cholesterol, LDL, HDL and Triglycerides using Erba Bioanalyzer. The serum Testosterone, Luteinizing Hormone (LH) and Follicle stimulating hormone (FSH) were estimated by Enzyme Linked Immunoassay (ELISA) colorimetric method in a 96 well plate AM 2100 microplate reader (Alere) using Krishjan Biosystems Kit. [43] at INVITOX R and D institute, Pune.

Statistical Analysis

Results are expressed as the mean ± Standard Error of the Mean (SEM). Statistical analysis was carried out by one way followed by Tukey's multiple range tests; and two-way Analysis of Variance (ANOVA) followed by Bonferroni post hoc test by using the software Graph Pad Prism trial version 5.0 (Graph Pad Software, Inc., La Jolla, CA, USA). A value of $p<0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION

Effect of IB and PL on Body Weight and Blood Sugar Level (BSL)

There were no significant changes were observed in the body weight of rats on every week. Significant reduction in BSL was observed with IB 2 (200 mg/kg), combinations groups and CC (100 mg/kg) compared to LTZ control (Fig. 1).

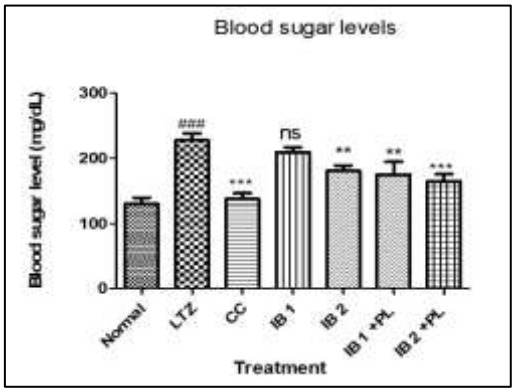
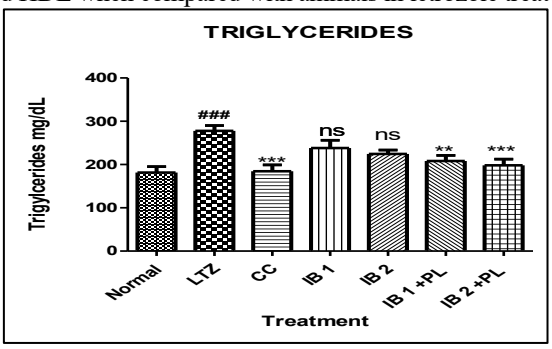


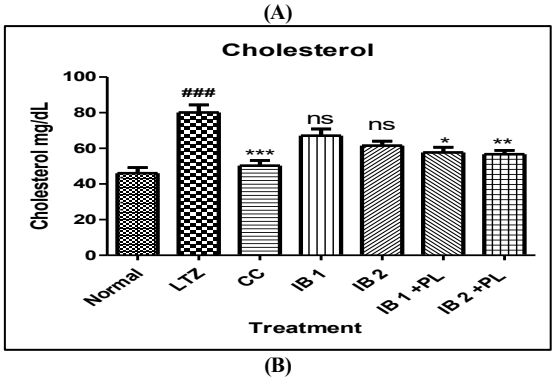
Figure 1: Effect of IB and combination groups on blood sugar level. Data was expressed as mean ± SEM (n= 6) Statistical significance was determined using one way ANOVA followed by Turkey test. ### $p<0.001$ compared to normal, *** $p<0.001$, ** $p<0.01$, ns Non significant compared with LTZ control.

Effect of IB and PL on Lipid Profile

Significant increase in serum triglycerides, cholesterol and LDL and decreased HDL concentration was found in the animals of control group treated with letrozole as compared to the animals in normal group. Treatment either with standard or test drug and its combination significantly reduced the concentration of serum triglycerides, cholesterol and LDL concentration and increased HDL when compared with animals in letrozole treated control group (Fig. 2).



(A)



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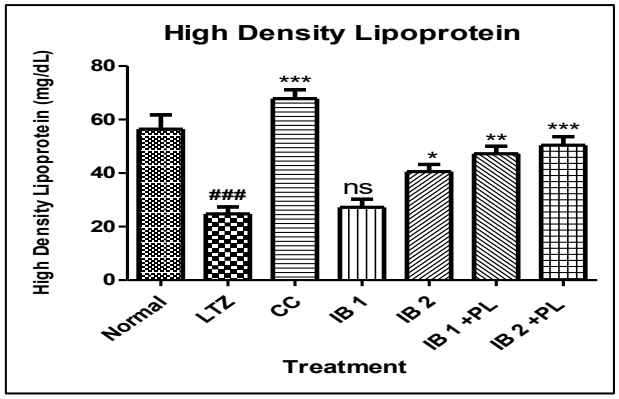

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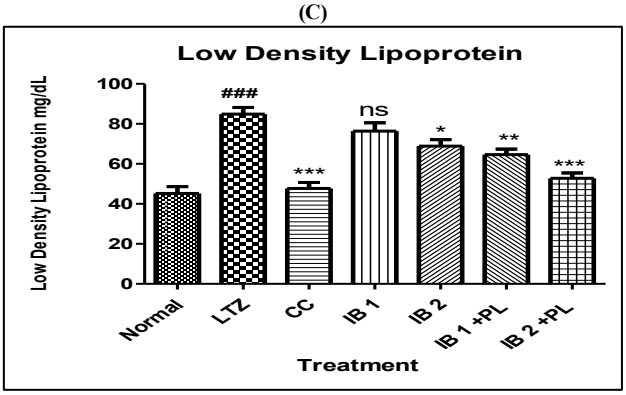
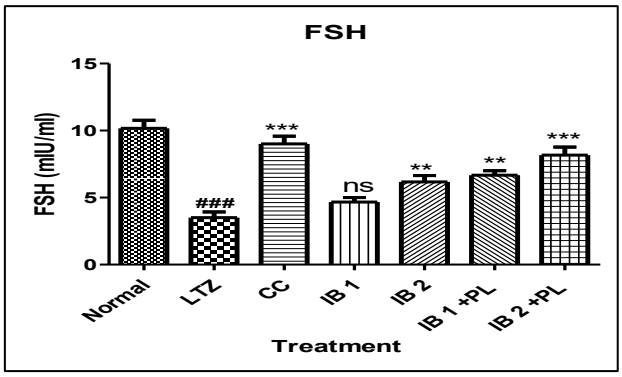


(D)

Figure 2: Effect of IB and combination groups on Lipid profile. A. Triglycerides; B. Cholesterol; C. High Density Lipoprotein; D. Low Density Lipoprotein. Data was expressed as mean ± SEM (n= 6) Statistical significance was determined using one way ANOVA followed by Turkey test. ### *p*<0.001 compared to normal, ***p<0.001, **p<0.01, *p<0.05 ns Non significant compared with LTZ control.

Effect of IB and PL on Serum Hormonal Profile

Significant reduction in FSH and AMH was observed in the animals of letrozole treated control group as compared to the animals in normal group. Whereas, the concentration of FSH and AMH in animals in standard, test groups and combination groups were found to be increased when compared with the animals in letrozole treated control group. From the Fig. 3, it is observed that there is a significant increase in the level of testosterone and luteinizing hormone in the letrozole induced control group. Treatment either with standard, clomiphene citrate, test groups or combination groups relapse these hormone concentrations as compared to the animals in control group (Fig. 3).



(A)

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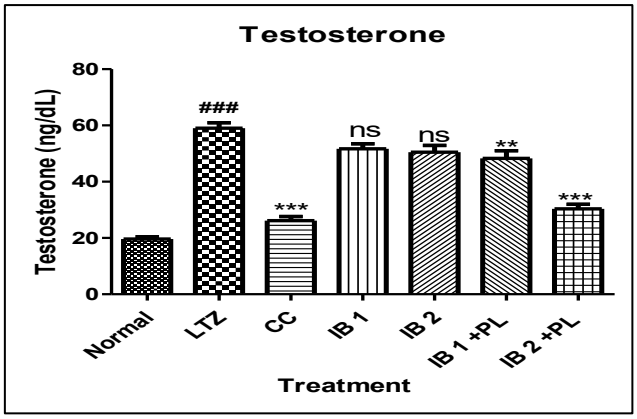

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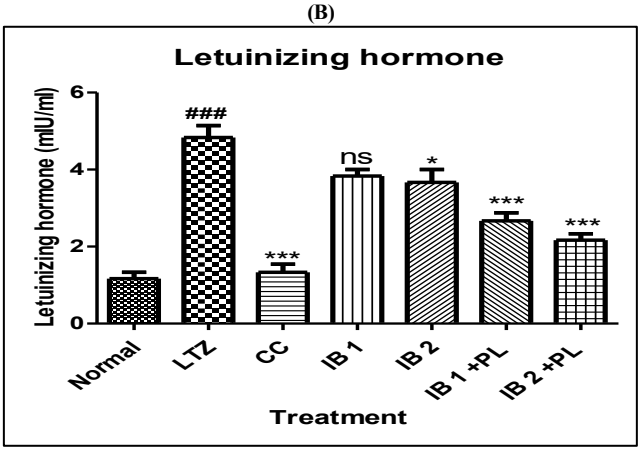

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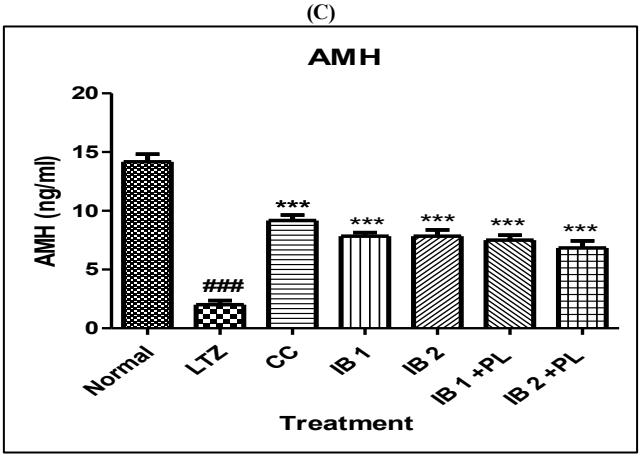

(D)

Figure 3: Effect of IB and combination groups on Hormonal profile. A. Follicle Stimulating Hormone (FSH); B. Testosterone; C. Luteinizing Hormone (LH); D. Anti Mullerian Hormone (AMH). Data was expressed as mean ± SEM (n= 6) Statistical significance was determined using one-way ANOVA followed by Turkey test. ### p<0.001 compared to normal, ***p<0.001, **p<0.01, *p<0.05, ns Non significant compared with LTZ control.

Effect of IB and PL on Ovary Weights

Weight of ovaries in the animals of letrozole treated control group was found to be significantly increased when compared with normal animals. Weight of ovaries in animals treated either with standard, test drug and combination groups was significantly reduced as compared to LTZ control (Fig. 4).

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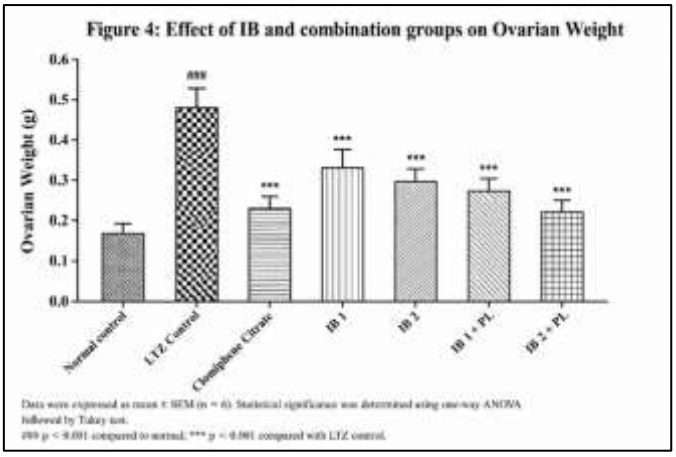

Figure 4: Effect of IB and combination groups on Ovarian Weight. Data was expressed as mean ± SEM (n= 6) Statistical significance was determined using oneway ANOVA followed by Turkey test. ### *p*<0.001 compared to normal, ****p*<0.001 compared with LTZ control.

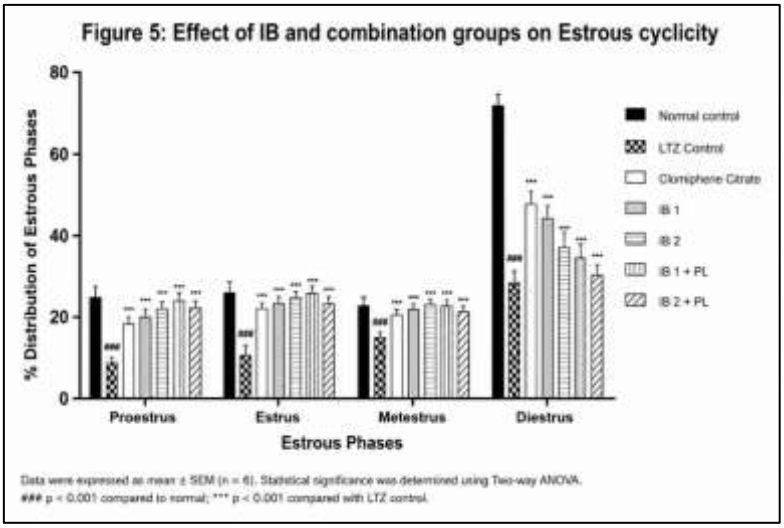

Figure 5: Effect of IB and combination groups on Estrous cyclicity. Data was expressed as mean ± SEM (n= 6) Statistical significance was determined using Tow-way ANOVA. ### *p*<0.001 compared to normal, ****p*<0.001 compared with LTZ control.

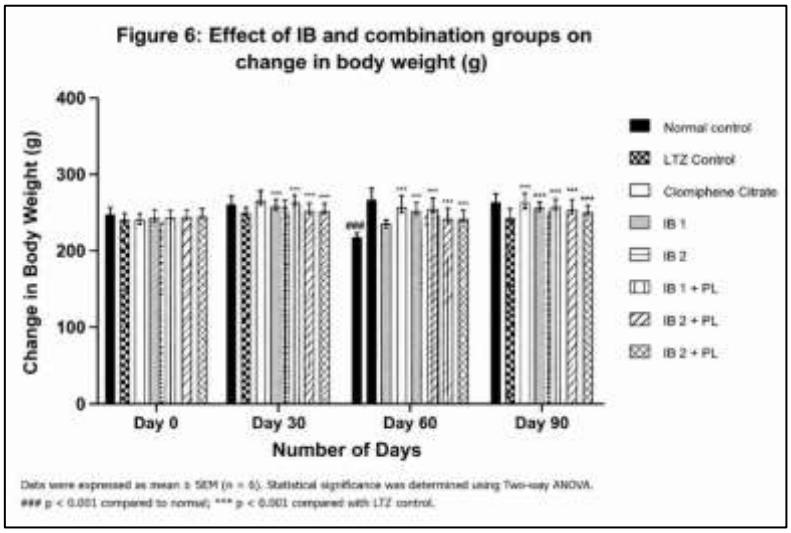

Figure 6: Effect of IB and combination groups on change in body weight (g). Data was expressed as mean ± SEM (n= 6) Statistical significance was determined using Tow-way ANOVA. ### *p*<0.001 compared to normal, ****p*<0.001 compared with LTZ control.

Histopathological Analysis

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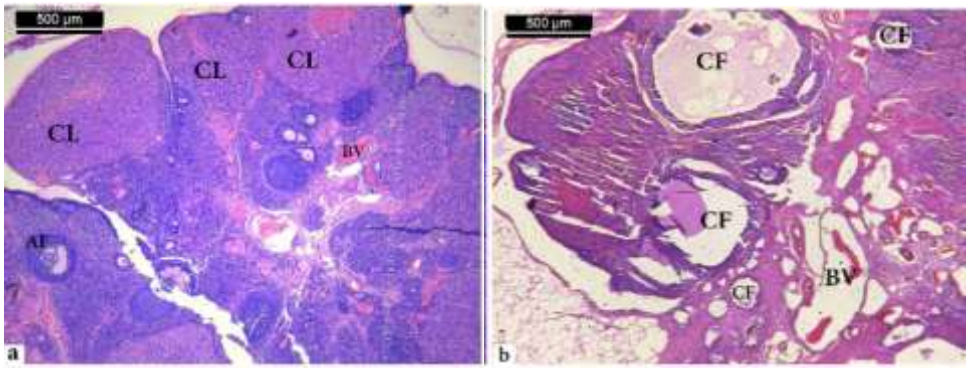
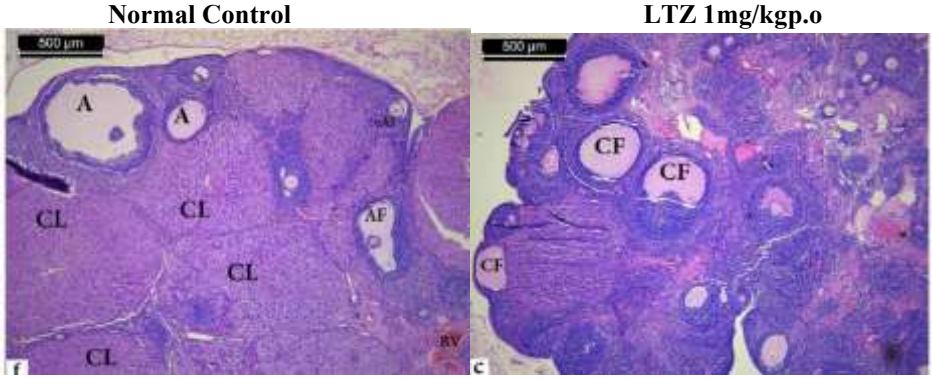
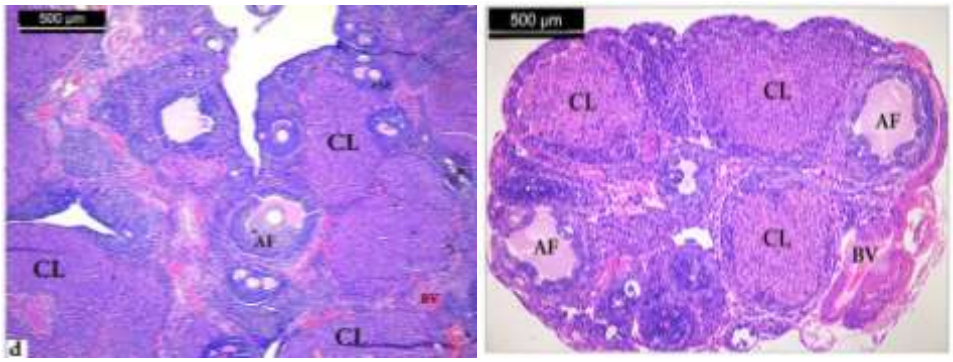


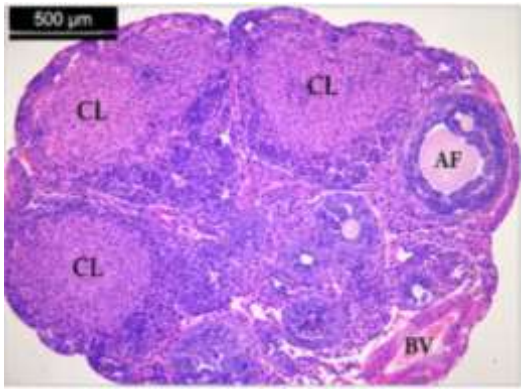
Normal Control **LTZ 1mg/kgp.o**



Standard **IB1**



IB12 **B 1 + PL**



IB 2 + PL

The ovaries' regular architecture, including the presence of healthy corpora lutea (CL) and growing follicles, suggests that ovulation and folliculogenesis are occurring normally.
Ovaries in the LTZ control group showed signs of PCOS induction, including numerous cystic follicles (CF), no corpora lutea, damaged follicular structure, and aberrant stromal tissue.

Follicle development, many corpora lutea, and a marked decrease in cystic follicles were all signs of ovulatory function recovery in the standard (clomiphene citrate) case.

IB1 (Ipomoea batata 100 mg/kg): Some cysts remained, but overall, things became better with less cystic follicles and the start of follicular development.

Follicle health, the return of corpora lutea, and the reduction of cystic follicles are all hallmarks of IB2 (Ipomoea batata 200 mg/kg), which promotes a more rapid recovery than IB1.

When administered together, IB1 and PL significantly reduced cyst formation, restored ovarian architecture with many corpora lutea and healthy antral follicles.

The group that did the best histologically was the IB2 + PL group. Their ovaries looked almost normal, with formed follicles, lots of corpora lutea, few cystic follicles, and recovered ovulatory activity. Ovarian morphology was improved in a dose-dependent way by Ipomoea batata, according to histopathological findings; however, restoration of ovarian structure and function was superior when combined with Piper longum in combination therapy. The effects of letrozole on polycystic ovary syndrome were reversed most effectively in the IB2 + PL group.

DISCUSSION:

Hyperandrogenism, insulin resistance, polycystic ovarian morphology, and ovulatory dysfunction are the hallmarks of polycystic ovary syndrome (PCOS), a complicated metabolic and endocrine condition [1–3]. There is a well-established experimental model for polycystic ovary syndrome (PCOS) in rats that is produced by letrozole. This model closely resembles the endocrine, metabolic, and ovarian abnormalities seen in patients with PCOS [42]. Androgen excess, disrupted folliculogenesis, anovulation, and cyst formation are side effects of letrozole, a non-steroidal aromatase inhibitor, which inhibits the conversion of androgens to estrogens [42]. Evidence of polycystic ovary syndrome (PCOS) including altered estrous cyclicity, hyperglycemia, dyslipidemia, hormonal imbalance, increased ovarian weight, and typical histological alterations in ovarian tissue was found in this investigation after letrozole therapy.

A key marker of reproductive health in rodents is estrous cyclicity. Anovulation and ovarian dysfunction were indicated by disturbed cyclicity and protracted diestrus in the letrozole-treated control group. When used alone or in conjunction with Piper longum, Ipomoea batata enhanced estrous phase distribution and brought cyclicity back to normal. The IB2 + PL group showed the largest improvement in restoration, which may indicate that their follicular maturation and ovulatory activity were better. These results show that the medication successfully mitigated the effects of letrozole on reproduction [3,5,42].

An overabundance of androgens in the ovaries is caused by polycystic ovary syndrome, which is often accompanied with hyperglycemia and insulin resistance [5,12,13]. Blood glucose levels were found to be considerably higher in animals that were given letrozole compared to animals that were not. Controlling blood sugar levels was a major goal of the clomiphene citrate, IB2, and combination treatment groups. The phenolic chemicals, flavonoids, and dietary fiber in Ipomoea batata enhance glucose consumption and insulin sensitivity, which may explain its antihyperglycemic action [26,27,38]. Reportedly, Piper longum also has antidiabetic effects and may improve glucose metabolism even more [18]. A synergistic interaction between the two plants is suggested by the better decrease reported in the combination groups.

A dyslipidemia profile including decreased HDL levels and increased triglycerides, total cholesterol, and LDL is typical of polycystic ovary syndrome (PCOS) [2,4]. The metabolic dysfunction was confirmed by the fact that the lipid parameters of the letrozole control group deteriorated significantly in this investigation. Reduced triglycerides, cholesterol, and LDL levels and increased HDL levels were results of enhanced lipid homeostasis brought about by treatment with Ipomoea batata and Piper longum. Both plants have bioactive components that may have antioxidant and hypolipidemic actions, which would explain the positive results [17,18,38]. The greatest significant improvement was observed with the IB2 + PL combination, suggesting that it provided better protection against PCOS-related metabolic abnormalities.

A hallmark of polycystic ovary syndrome is hormonal imbalance [3]. While concentrations of FSH and AMH were reduced in the rats treated with letrozole, levels of testosterone and LH were markedly increased. Follicle arrest and cyst development are worsened when the production of androgens by ovarian theca cells is stimulated by elevated LH [12]. Levels of testosterone and LH were markedly decreased by clomiphene citrate and Ipomoea batata treatment, whereas levels of FSH and AMH were markedly increased. Improvements in folliculogenesis and normalization of the hypothalamic-pituitary-ovarian axis function may be indicated by the restoration of these hormonal markers [3,5,13]. When compared to other treatment groups, the IB2 + PL combination showed the most improvement, coming close to the response seen with clomiphene citrate [41].

Follicle cysts and stromal hypertrophy cause PCOS symptoms, including enlarged ovaries [3,42]. Ovarian weight was found to be considerably higher in the group that received letrozole as compared to the control group that received no treatment. The combination therapy consisting of clomiphene citrate, Ipomoea batata, and other agents considerably decreased ovarian weight, which showed that cyst formation was inhibited and normal ovarian physiology was restored. The groups that received a combination of treatments, namely IB2 + PL, showed the greatest reduction.

The results from the biochemistry and hormone analyses were corroborated by histopathological examinations. The letrozole control group's ovaries confirmed the successful development of polycystic ovary syndrome (PCOS) with numerous cystic follicles, altered ovarian architecture, and the absence of corpora lutea [42]. Ipomoea batata treatment improved ovarian morphology in a dose-dependent manner, with fewer cystic follicles and the return of developing follicles. Histologically, patients who received combination therapy with Piper longum showed a marked improvement, with many corpora lutea, healthy follicles, and an ovarian architecture that was almost normal. When compared to the other groups, the IB2 + PL group showed the biggest improvement in ovarian shape and ovulatory activity, indicating the greatest treatment efficacy.

The results show that Ipomoea batata has a strong protective impact against letrozole-induced polycystic ovary syndrome (PCOS), and when paired with Piper longum, these effects are much stronger [17,18,38]. Evidence from glycemic control, lipid metabolism, hormonal balance, ovarian weight, and histological architecture, among other areas, shows that the combo therapy successfully improves PCOS-related metabolic and reproductive problems. The combination of IB2 and PL showed the most therapeutic benefit of all the experimental groups, suggesting that this herbal approach could be a beneficial one for PCOS therapy.

CONCLUSION:

Letrozole effectively caused polycystic ovary syndrome (PCOS) in female Wistar rats, as shown by problems with estrous cyclicity, hyperglycemia, dyslipidemia, hormonal imbalance, increased ovarian weight, and the creation of distinctive ovarian cysts. There was a dose-dependent improvement in these pathological changes after treatment with Ipomoea batata. When used together, Ipomoea batata and Piper longum were more effective than either herb alone. Following the test treatments, the following improvements were observed: normalized reproductive hormone levels, decreased ovarian weight, restored estrous cyclicity, lowered blood glucose levels, better lipid profile, and improved overall health. Reduction of cystic follicles and reawakening of corpora lutea were further validated by histopathological examination, confirming recovery of ovarian architecture. Results were similar to those of the gold standard medicine clomiphene citrate in the IB2 + PL group (Ipomoea batata 200 mg/kg + Piper longum 200 mg/kg), the experimental group with the most noticeable improvement. Results like these point to the combo therapy's efficacy in addressing PCOS-related metabolic and reproductive issues. Consequently, a potential and risk-free herbal treatment approach for PCOS control and ovarian function restoration could be Ipomoea batata combined with Piper longum.

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CONFLICT OF INTEREST:

The authors report no financial or any other conflicts of interest in this work.

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