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Evaluation of Sesame Seed Oil on Glucose, Lipid and Ovarian markers in Letrozole Induced PCOS Rats

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Abstract: Polycystic ovary syndrome is the globally prevalent endocrine disorder of reproductive aged women. The etiology of PCOS remains weakly defined, and therapeutic interventions are needed to improve understanding of the core pathophysiology of PCOS. In recent years, bioactive natural compounds have emerged as potential alternatives for PCOS management. *Sesame seed oil* has shown the remarkable anti-inflammatory, anti-allergic, and anticancer properties. The present study assessed the therapeutic efficacy of *Sesamum indicum L. oil* on metabolic and reproductive aspects in letrozole-induced PCOS rats. This study was conducted on 24 female *Wistar Albino* rats that were randomly divided into group I (control; n=6) and group II (experimental; n=18). Rats in group II were administered with 1mg/kg of Letrozole for 21 days to establish the PCOS model. After 21 days, group II rats were further divided into 3 groups and the groups were labeled as letrozole, metformin (50mg/kg) and sesame oil (300mg/kg) group. Following treatment for 21 days, blood samples were collected for FPG, Insulin, HOMA, testosterone and lipid profile and ovarian tissues were excised for histomorphological changes. Administration of sesame seed oil restored regular estrous cyclicity and significantly reduced FBG and testosterone levels with an insignificant decrease in insulin and HOMA-IR. Also, it significantly improved lipid profile, except LDL-C. Histopathological examination demonstrated a marked reduction in polycystic ovarian morphology, resembling normal ovarian architecture. The overall findings showed evidence of positive effects of *Sesame seed oil* on PCOS-associated pathophysiology by improving ovarian function in PCOS rats.

Keywords: Letrozole, PCOS, Sesame seed oil, ovaries, Glucose, testosterone

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Introduction

Polycystic ovarian syndrome (PCOS) is the worldwide prevalent endocrine dysfunction ranging from approximately 2.2%-26% in the reproductive women [1]. Hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology (PCOM) constitutes the pathophysiological features of PCOS that are frequently accompanied with insulin resistance, impaired glucose tolerance and obesity. This syndrome is associated with several comorbidities such as infertility, type 2 diabetes mellitus, depression, endometrial carcinoma, and metabolic dysfunction. The regulatory axis between the hypothalamus, pituitary gland, and ovaries is altered, thereby contributing to hormonal dysregulation in PCOS women. The therapeutic strategies primarily include lifestyle as well as pharmacological interventions that are often costly and may induce adverse effects, including gastrointestinal disturbances and weight gain [2]. On account of these limitations, herbal medicine has been emerged

as a promising alternative treatment modality for the management of PCOS. Phytochemicals extracted from medicinal plants have demonstrated effectiveness in improving the adverse effects associated with conventional pharmacotherapy. Scientific evidences suggest that bioactive compounds such as flavonoids, polyphenols, phytoestrogens, polyunsaturated fatty acids (PUFAs), and other plant-derived metabolites alleviate the clinical manifestations of PCOS [3].

Sesamum indicum L. is one of the prominent oilseed crops abundantly found in the African and Asian countries. Sesame seed oil holds the universal importance for its economic and human nutritional value. A study conducted by Fukuda and his colleagues has shown that these seeds provide considerable amounts of proteins, carbohydrates and oil [4]. These seeds are a rich source of bioactive constituents that are used as antiseptics, disinfectants, anti-tubercular agent's bactericides [5]. Due to its rich composition of phytochemical antioxidants including lignans (sesamin, sesamol, sesamolin), tocopherols, phytosterols and essential unsaturated fatty acids and balanced oleic-to-linoleic fatty acid ratio enhances the protective role of these seeds on human health. Recent researches have shown the protective effects of SSO against cardiovascular, metabolic, and coronary disorders [6,7]. Sesame has been used for the management of reproductive disorders such as oligo-menorrhea, prevention of fetal abortion, enhancement of sexual drive, and stimulation of sperm production [8]. Despite these ethnomedicinal claims, scientific evidence regarding its influence on menstruation remains limited [9]. The current study was designed to evaluate the potential therapeutic benefits of sesame seed oil on biochemical and histological changes in letrozole induced PCOS animal model.

Material and Methods

Chemicals

Analytical grade chemicals and Letrozole (LTZ) and Metformin were obtained from the Sigma-Aldrich.

Preparation of Sesame seed oil

Sesamum indicum seeds were obtained from a herbal medicinal store and were validated from the Botany Department, University of Karachi, Karachi, Pakistan. The dried seeds were then ground, and the powder was passed from 16- and 32-mesh sieves to acquire a 0.5-mm particle size. Powdered dried seeds were stored in a refrigerator at 4°C until use. Sesame seed oil was obtained via cold mechanical compression of the seeds, a method that involves the application of pressure to squeeze out the oil from the plant material. The oil was expressed from 1 kg of seeds using an oilseed expeller followed by filtration and bottling to yield 320 g, which is equivalent to 32 g % on a dry weight basis [10].

Animals

All experimental protocols were performed after the approval of Ethical Committee of Animal Care and Use of University of Karachi, Karachi, Pakistan. Cyclic, female Wistar Albino rats (100-120 g) were selected and purchased from the ICCBS (International Center for Chemical and Biological Sciences) and were housed in the animal house of the Department of Physiology, University of Karachi. Rats were placed in standard cages with a controlled environment and 12-h light/dark cycle. They were allowed to acclimatize for 2 weeks and were given a standard diet and water throughout the study period. Estrous cycle regularity has been checked using vaginal smear technique for all rats.

Study Design

A total of 24 female rats were allocated to 4 groups; each comprised of 6 rats. The rats in group 1 served as the negative control (normal) and received a daily oral dose of 0.9 % saline (1mg/kg body weight) for 60 days. For the PCOS induction, the rats in groups 2 to 4 received LTZ 1 mg/kg dissolved in 0.9% saline once daily orally for 21 days. After the confirmation of PCOD induction, these rats were randomly separated into three groups:
Group II, which served as the positive control (PCOS), continued to receive Letrozole and
Group III, received Metformin orally at a dose of 250 mg/Kg by dissolving it in 0.9% normal saline.
Groups IV was treated with *Sesamum indicum* seeds oil at dose of 1 ml/kg.
On day 51^{th} of the study period, 24 h following last treatment, rats were anesthetized, blood samples were collected in gel separator tubes and centrifugation was done to collect serum samples and stored at –80°C for biochemical analysis. Histomorphological examination was performed on ovarian tissues that were excised, cleaned and stored in 10% neutral buffered formalin.

Body weight Measurement
All the animals were weighed weekly throughout the experiment, and the weight of each rat was kept in record. At the end of the treatment period, body weight change was calculated.

Biochemical Estimations
The levels of serum total testosterone and insulin were measured using a commercial ELISA Kit whereas glucose and Lipid profile (cholesterol, triglycerides, and HDL-cholesterol) were evaluated using Global kits.
HOMA, LDL and VLDL were calculated using these formulas:
HOMA = [fasting insulin (μU/ml) x fasting glucose (mg/dL)] / 405; [11]
LDL = total cholesterol – (HDL + VLDL); [12] and
VLDL = triglycerides/5; [13]

Histopathological examination
Ovaries from each group were collected, fixed and processed to produce paraffin-embedded sections (5-μm- thick) that were later stained with hematoxylin and eosin stain to examine the histomorphological characteristics of ovaries. The number of follicular cysts, corpus luteum, graffian, antral and atretic follicles, and thickness of the granulosa and theca cell layers were analysed using image analysis software.

Statistical analysis
Statistical analysis was performed by using SPSS software version 22. Results were expressed as mean ± standard error of mean (SEM). Data was analyzed by using ANOVA to test the significant differences ($P < 0.05$) in the groups. Also, Tukey's post hoc test was used to check the inter group comparison. (*) represents statistically significant difference between the groups at $P < 0.05$. Graphs were created using Microoft Excel for Windows.

Results
Body Weight in Control and Experimental Groups

As shown in Figure 3.1, rats administered with letrozole showed an increase in the weight of the animals in a time dependent manner as compared to the control group animals. The body weight of *Sesame* seed oil treated rats revealed insignificant effect whereas metformin group showed significantly lower body weight in contrast to LTZ group. Control group showed increased body weight with the passage of time but in treatment groups a trend followed decline in body weight was observed.

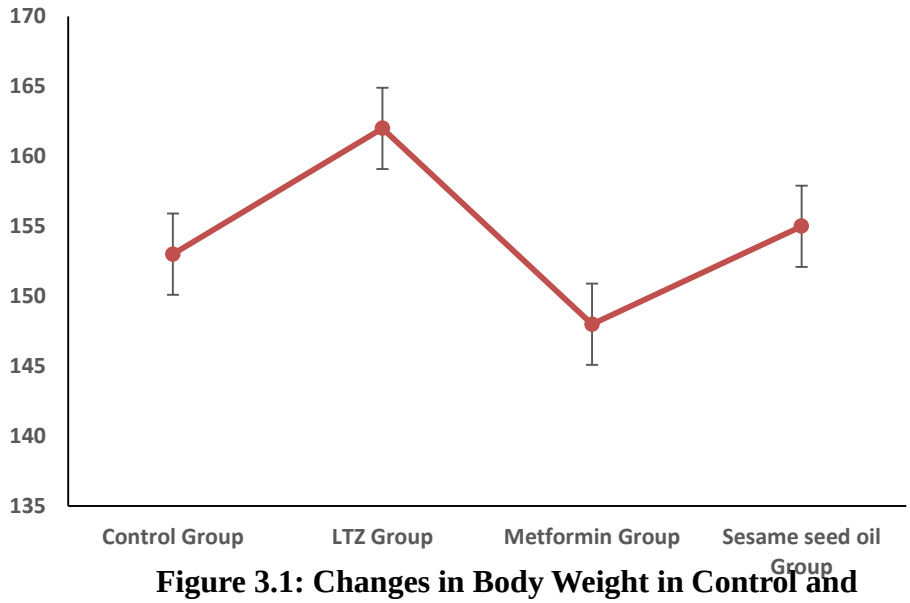


Figure 3.1: Changes in Body Weight in Control and Experimental rats

Effect on Estrus cycle observed in control and Experimental Groups

The Estrous cycle of the letrozole administered group is altered in contrast to the control group in which the estrus cycle is occurring in a normal pattern ($p < 0.05$); (Fig. 3.2). This is due to the effects of letrozole which causes hormonal disturbances that ultimately lead to the alteration of the estrus cycle. As mentioned earlier that letrozole is an aromatase inhibitor, so it inhibits the aromatization of androgens and thus declines the levels of estrogen. It also increases the levels of T2 which is an underlined cause of PCOS. The result indicates that the estrus cycle of PCOS induced rats was normalized after treatment. The mean values of the control group and the metformin-treated group shows that there is only a slight difference between the regularity of the estrus cycle i.e. the metformin-treated group shows a regular estrus cycle but its regularity is not similar to control group rats because the metformin-treated group was first administered by letrozole to induce PCOS. On the other hand, the sesame oil-treated group also showed the estrus cycle regularity but the ratio is slightly lower than the other two groups.

It has been shown in Figure 3.2 A, predominantly corpus luteum and primordial follicle and mature follicles were observed. Figure 3.2; B is the ovarian section of the LTZ group in which cystic corpus luteum or occasional cystic follicles and some immature cysts and atretic follicles were more frequently seen. In figure C, the ovarian section has been taken from the metformin-treated group rat, a healthy corpus luteum can be seen with growing follicles. Figure D shows the ovarian section of

sesame oil-t healthy and some immature

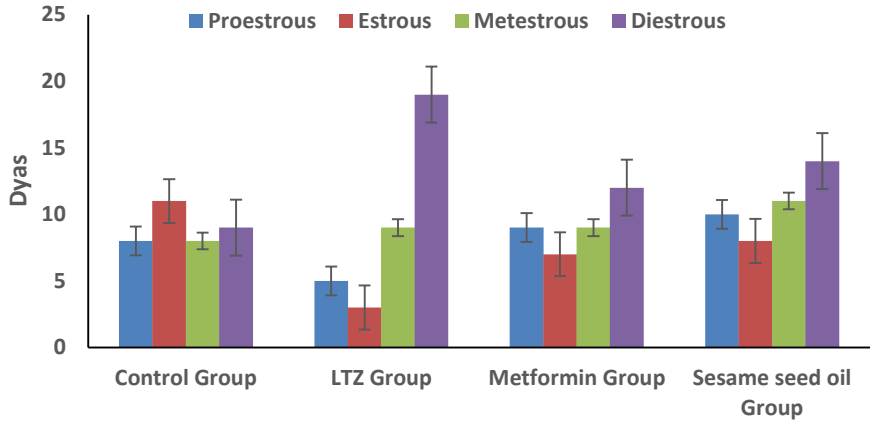


Figure 3.2: Phases of Estrous Cycle in Control and Experimental rats

Histological analysis of ovaries in control and Experimental Groups

It has been shown in Figure 3.2 A, predominantly corpus luteum and primordial follicle and mature follicles were observed. Figure 3.2; B is the ovarian section of the LTZ group in which cystic corpus luteum or occasional cystic follicles and some immature cysts and atretic follicles were more frequently seen. In figure C, the ovarian section has been taken from the metformin-treated group rat, a healthy corpus luteum can be seen with growing follicles. Figure D shows the ovarian section of sesame oil-treated rats in which a healthy corpus luteum could be seen along with healthy and some immature follicles.

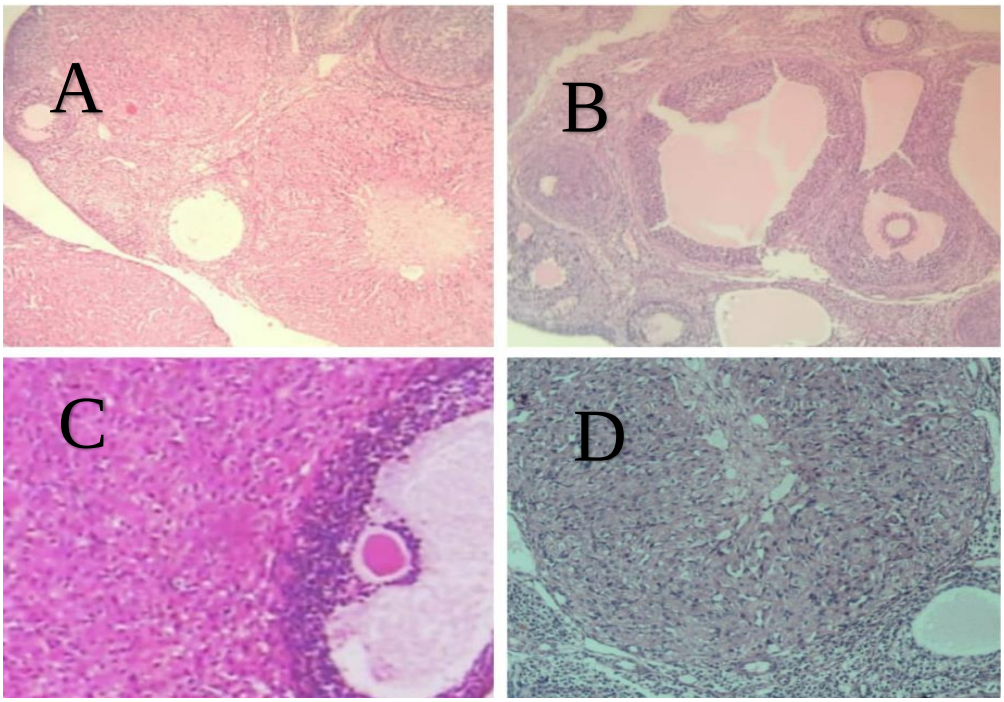


Figure 3.3 (A-D): Histomorphological differences among the ovarian sections of all four experimental groups. Key: A: ovarian section of the control group; B: ovarian section of Letrozole

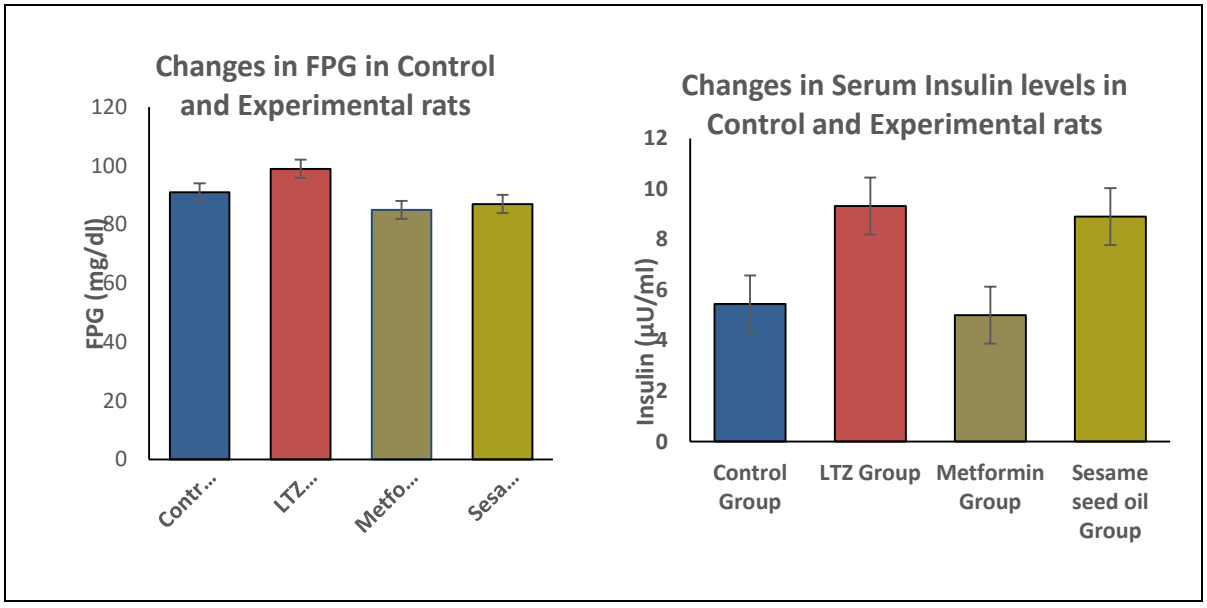
induced PCOS animal model. C: ovarian section of Metformin-treated rat; D: ovarian section of Sesame seed oil treated rat.

Hormonal and Biochemical profiles in control and Experimental Groups

Fig. 3.4 shows hormonal and biochemical estimations of glucose, insulin, testosterone and lipid profile estimations in the control and intervention groups. (Fig. 3.4; A) shows the fasting plasma glucose levels in the studied groups. Rats treated with LTZ exhibited higher glucose levels than control rats ($p < 0.05$). Treatment with sesame seed oil and metformin significantly brought down the high levels of glucose in PCOS induced rats. Fig 3.4 (B) shows that maximum insulin secretion was significantly observed in the LTZ group compared to the control group ($p < 0.05$). Sesame seed oil at a dose of 1mL/kg did not significantly improved the serum insulin levels toward their normal levels. Additionally, HOMA-IR did not show significant difference between sesame seed oil intervention and control group ($p > 0.05$). Furthermore, metformin treatment group was superior to sesame seed oil group in the restoration of serum insulin levels and HOMA-IR ($p < 0.05$).

As presented in Figure 3.4 (C), in the LTZ group, the testosterone levels were remarkably higher in contrast with the control group ($p < 0.05$). Conversely, the rats treated with sesame seed oil at dose of 1 mL/kg exhibited significantly reduced testosterone levels compared with the LTZ group ($p < 0.05$). The metformin group exerted superior hormonal effects comparable to sesame seed oil group ($p < 0.05$).

Lipid profile (Fig. 3.4; D) evaluation in the LTZ group exhibited significantly altered levels than the control group ($p < 0.05$). With regard to the sesame seed oil group, the lipid profile demonstrated significantly lower values compared with the LTZ group ($p < 0.05$) except



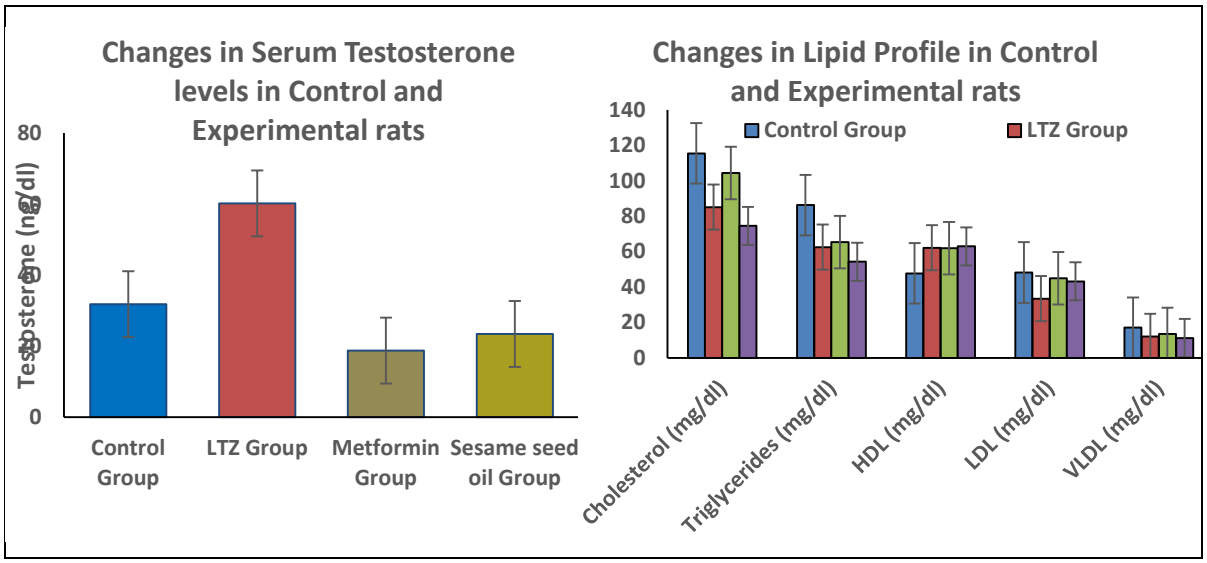


Figure 3.4 (A-D): The changes in fasting plasma glucose, insulin and testosterone levels and Lipid Profile in each group during PCOS induction and treatment period.

LDL ($p > 0.05$). Treatment group of metformin also showed the significant effects on lipid levels in contrast to LTZ group ($p < 0.05$).

Discussion

PCOS is the leading endogynecological disorder in reproductive-age females all over the world. The exact or the underline cause of the disease is still unclear but it can be said that hyperandrogenism and I.R are the major factors that contribute to this syndrome [14]. There are many pharmaceuticals and non-pharmaceutical approaches that have been proposed to treat PCOS. In the present study, we assessed the curative effects of sesame seeds oil on the hormonal and biochemical disturbances that are caused by PCOS. The parameters that were examined in this study include, body weight, hormonal estimations including testosterone and insulin, lipid profile and estrus cyclicity by vaginal smears.

The experimental induction of letrozole induced PCOS in rats depicted hallmark features of this disorder, including hyperandrogenism, ovarian cyst formation, abnormal follicular development, and hyperglycemia. Letrozole suppresses the conversion of androgens to estrogens, thereby elevating circulating androgen concentrations. This hyperandrogenic state disrupts the estrous cycle, contributes to follicular atresia and disturbed follicular morphology. This study also demonstrated similar outcomes in LTZ induced PCOS rats that is consistent with the prior studies, such as the occurrence of prolong diestrous phase, increased serum testosterone levels, and ovarian cyst formation [15,16].

In the current study, PCOS induction led to a significant increase in body weight which is in concordance with the earlier researches that reported the elevation in body weight in letrozole-induced PCOS rats, comparable to the clinical presentation of PCOS women. Furthermore, treatment of PCOS rats with sesame seed oil exerted no significant influence on body weight. A recent research study revealed that administration of sesame oil in both male and female rats for 21 days exhibited no significant change in body or ovarian weight, which is in concordance with the findings of our study. However, when PCOS rats were treated with metformin, a significant decrease in body weight was found [17].

The observed prolongation of the diestrous phase in rats administered letrozole showed the disruption in estrous cyclicity. This could be due to alterations in circulating gonadotropins and sex steroid hormones, or alone may be attributable to increased circulating testosterone that is essential for maintaining ovarian physiology, including ovulation and follicular maturation. Sesame seeds, rich in lignans such as sesamine and sesamolin with known estrogenic properties, reduced the proportion of vaginal diestrous days, likely through attenuation of testosterone levels. These phytoestrogens can modulate adrenal steroidogenesis in male rats or via their estrogenic metabolites or by mimicking endogenous estrogens, have the capacity to reduce testosterone which corroborate the findings observed in our investigation [17,18].

The ovarian sections of control rats exhibited normal cortical and medullary structure with follicles at various stages of development and multiple corpora lutea. In contrast ovarian tissues of letrozole administered group, increased number of cystic follicles, small follicles, absence of graffian follicle and decreased number of corpus luteum were observed which proves the fact that letrozole administration inhibits aromatization which leads to the occurrence of cystic ovaries [19]. Metformin and sesame oil treated ovarian sections were somewhat similar to that of the control group. Treatment with sesame seed oil or metformin markedly reduced the number of cystic follicles, restored multiple corpora lutea and promoted the presence of antral follicles at different stages of maturation Sesame seed oil enhanced folliculogenesis, thereby mitigating ovarian dysfunction associated with the disorder [20].

In the present study, testosterone concentrations were markedly elevated in letrozole-treated rats compared with controls [21]. These alterations are attributable to aromatase inhibition, letrozole impedes the conversion of androgen precursors into estrogens, thereby promoting androgen accumulation which diminishes estrogen synthesis within the hypothalamus and pituitary. The subsequent decline in estrogen-mediated negative feedback augments the secretion of LH, thus promoting the observed hormonal imbalance in PCOS women [22]. Moreover, our study found that administration of sesame seed oil in PCOS induced rats normalized the serum testosterone levels. Wu and colleagues also reported that sesame suppress the levels of testosterone through lignans that binds to estrogen receptors on adrenocortical cells and thus contributes to the alleviation of hyperandrogenism in PCOS patients [23]. In addition, sesame seeds contain stigmasterol and β-sitosterol, both of which possess anti-androgenic properties that lower testosterone by interfering with the dihydrotestosterone–receptor complex. Plant-derived phytoestrogens, including those present in sesame, further decrease testosterone concentrations via negative feedback on luteinizing hormone (LH). Consequently, reduced androgen levels diminish LH secretion, thereby weakening its regulatory influence on follicle-stimulating hormone (FSH) [25,24]. Metformin significantly decreased the levels of testosterone showing contributing to the improvement in obesity, hyperinsulinemia and insulin resistance [26].

The present study found the high Insulin levels observed in the LTZ group in contrast to the control group rats. Serum Levels of insulin in the control and the metformin-treated groups were approximately similar as metformin enhances the level of insulin sensitivity in PCOS [27,28]. Further, in sesame seed oil group, reduction in serum insulin levels revealed statistically insignificant alterations which are similar to earlier researches [29,30].

Biochemical analysis was also performed to compare the results between the control and the experimental groups. The elevated blood glucose levels were observed in letrozole induced PCOS rats which may be attributed to insulin insensitivity. Rats treated with sesame seed oil exhibited significant reductions in glucose levels which might be due to β-cell regeneration [28]. Administration of letrozole altered lipid profiles in the PCOS induced rats. This study showed that

treatment with sesame seed oil resulted in a significant reduction in the levels of Cholesterol and triglycerides with a statistically significant increase in serum HDL levels. These results support the previous research showing the antihyperlipidemic effects on patients with hypercholesterolemia post intervention with sesame seeds [31,32]. Rats treated with metformin markedly exhibited the improvement in the lipid levels which shows the restoration of normal morphological and physiological functions in the PCOS treated rats [33].

Conclusion

The present investigation highlighted that sesame seed oil ameliorate the PCOS manifestations by regulating the testosterone, glucose and lipid levels. Despite the absence of significant effects on insulin, LDL and body weight, it is important to note however, that regular estrus cycles were observed subsequent to the administration of sesame oil. Hence this research proposed that supplementation of sesame seed oil exerts therapeutic effects on reproductive functions in PCOS women.

Future Perspectives

Further researches are required to explore the mechanism of action of sesame seed oil on key ovarian biomarkers at both cellular as well as molecular levels.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

All experimental protocols were performed after the approval of Ethical Committee of Animal Care and Use of University of Karachi, Karachi, Pakistan.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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None

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