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Evaluation of the Therapeutic Potential of Flaxseed's in Letrozole-Induced Polycystic Ovary Syndrome in Rats by Histology

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تقييم الإمكانات العلاجية لحبيبات الكتان في متلازمة تكيس المبايض الناتجة عن الليتروزول في الجرذان عن طريق الأنسجة

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a metabolic condition that impacts females during their reproductive years. PCOS is marked by the presence of multiple cyst-like follicles on the ovaries, irregular or absent ovulation, and resistance to insulin. This research seeks to investigate the consequences of flaxseed extract on the ovary in the PCOS rat's model by histological techniques and serum hormone level.

Materials and Methods: Sixteen female albino rats (6–8 weeks old, estrous cycle in female rats repeats every 4–5 days) were assigned to four groups: the first group was the control, second group received 0.2 mg/kg body weight of letrozole by gavage, the third group was given 100 mg/kg body weight flaxseed extract intraperitoneally, and the mixed group received both letrozole and flaxseed daily for 21 days. The total period of the study was 2 months, including 15-20 days for preparation, 21 days for animal experimentation, and 20 days for histological and statistical analysis.

Results: Histological examination of the ovary revealed letrozole-induced ovarian cysts and disruption of follicles. Flaxseed treatment significantly restored ovarian morphology, with a recovery of follicular development. Hormonal assay indicated that testosterone and AMH were elevated, while estrogen and progesterone were decreased in the letrozole group to other groups. Extraction of flaxseed supplementation restored hormonal equilibrium, lowering testosterone and increasing estrogen and progesterone.

Conclusion: These results demonstrate that flaxseed extract may offer a potentially effective treatment option for PCOS through modulating ovarian and endocrine dysregulation.

Key words: Ovarian cysts, Flaxseed, PCOS, Letrozole, antioxidant, female rat, histological study.

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1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is a reproductive and endocrine condition, impacting between 5 and 20% of women globally throughout their reproductive years [1, 2]. PCOS's primary pathophysiologic characteristic is elevated testosterone that leads to hyperandrogenism [3], erratic menstrual cycles and overgrowth of hair, sometimes it will cause more serious issues like infertility and problems throughout pregnancy [4].

The cessation of oogenesis is indicated by hyperplasia and a large number of immature and atretic follicles [5]. PCOS happened when gonadotropin-releasing hormone (GnRH) was more frequently from the hypothalamus. This increase raises elevations of luteinizing hormone (LH) and lowers concentrations of follicle-stimulating hormone (FSH), high level of LH can lead to excess production of androgen hormones like testosterone, while lower FSH causes problems like follicular arrest and cyst formation, resulting in irregular periods. Additionally, the feedback from sex hormones (estrogen and progesterone) is reduced [6, 7].

One of the medications is used widely by women and causes PCOS is Letrozole. Chemically, Letrozole appointed as 4,4′-(1H-1,2,4-Triazol-1-ylmethylene) dibenzonitrilean, inhibitor of non-steroidal aromatase that inhibits aromatization of the entire body, paracrine signaling, oogenesis and ovarian function [8]. Also, it has become a potential treatment for various gynecologic conditions, and its indications for usage in treating certain hormone receptor dependent ailments in premenopausal females, like uterine fibroids and endometriosis, have expanded. [9]. However, the study exhibited cystic follicles with interstitial cell hyperplasia, ovarian hyperandrogenism in letrozole revealed females fulfilling the physical characteristics of PCOS [5].

Nowadays, a lot of people employ plant extracts to treat female reproductive disorders one of them is flaxseed. Flaxseed’s scientific name is Linum usitatissimum L., it is a member of the linaceae family, is recognized for its rich nutrient profile, including fiber, minerals, vitamins, and lignans, which contribute to its numerous health benefits [10, 11]. In particular, flaxseed’s high lignan content can influence estrogen synthesis by modulating enzymes like aromatase and reduce androgen levels by inhibiting 5α-reductase, which converts testosterone to dihydrotestosterone [12]. Additionally, flaxseed may improve endocrine function and regulate female sex hormones, making it beneficial for conditions like PCOS. However, it also contains antinutritive substances, for instance phytic acid and cyanogenic glycoside, that should be considered when consuming flaxseed [13]. Therefore, the current study was created to

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investigate the likely effects of flaxseed extract on the histopathological and hormonal findings of a letrozole-induced PCOS rat model.

2. MATERIALS AND METHODS

2.1. Research Animals

In the ongoing investigation, we employed 16 mature rats; all were (6–8 weeks old, estrous cycle in female rats repeats every 4–5 days well and weighed between 150 and 200g. These animals were reared and maintained in groups of four rats/cage at an animal house belonging to the department of Biology, College of Science, Salahaddin University - Erbil, Erbil, Kurdistan region, Iraq. The temperature was kept between 24 and 30 degrees Celsius. The animals were provided a normal rat diet.

2.2. Letrozole Dose

Letrozole was purchased from a pharmacy in Erbil city Kurdistan region-Iraq. There was a 2.5 mg pill available, the pills were crushed then liquefied in oil, at an amount of 2 mg/kg body weight.

2.3. Flaxseed Extracts Preparation

Flaxseed, which is readily available in the market, is utilized to prepare the extract. The flaxseeds were totally processed into powder in a grinder. We soak 20 grams of flaxseed powder in 100 milliliters of hot distilled water for (30) minutes. After socking, filteration the flaxseed-soaked distilled water to extract the beneficial components of flaxseed in their purest form. The aqueous extract of flaxseed employed in this study was produced as a filtered slimy solution [15].

2.4. Experimental Design

The protocols of animal experiments were approved by the animal house belonging to Biology department College of Science, Salahaddin University - Erbil Kurdistan-Iraq Ethical Committee (ethics number: 4S/298). Sixteen healthy 6–8 weeks old, estrous cycle in female rats repeats every 4–5 days and weighed between 150-200gm were randomly assigned to four groups. The first group was given normal saline by intraperitoneal injection and the second group was given letrozole (2 mg/kg/body weight (b.w)) by gavage. The third group of rats was given flaxseed extract (100mg/kg/b.w) by intraperitoneal injection. And the last group, rats, were given a mixture of letrozole (2 mg/kg) and flaxseed extract (100mg/kg/b.w) daily for 21 days.

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2.5. Body Weight

At the start and finish of the trail, the weight of the rats' bodies in each group was measured, then the body weight (BW) gain (in grams) was calculated as follows: Body weight gain = finish BW – initial BW. Such gaining BW was enrolled for every rat separately [16]

2.6. Dissecting Anesthesia and Removing Ovaries

Ketamine hydrochloride 80 mg/kg (Trittau, Germany) and xylazine 12 mg/kg (Interchem, Halland) were injected intraperitoneally into the rats. Then the rat ovaries were fixed in the 10% buffered formalin fixative after being slaughtered and having their ovaries removed.

2.7. Histological Preparation

Sections of ovaries were promptly preserved in 10% neutral buffered formalin. The fixed samples were dehydrated in increasing ethanol grades, cleaned in xylene, infiltrated, and embedded in paraffin at 60ºC. For the purpose of investigating the histological examinations, 4-6 µm thicknesses of the ovary were cut using a rotating microscope (bright, MIC) and regularly stained with hematoxylin and eosin (H&E) [17]. The samples were inspected and photographed using a light microscope (a digital binocular compound microscope with a built-in 3MP U 3 camera).

2.8. Blood Collection and Hormone Assay

Following treatment, rats' hearts were punctured to collect blood into tubes devoid of EDTA for the biochemical testing. The tubes were then centrifuged (Beckman J2-21 manufactured by Beckman Coulter) at 3000 rpm for 15 minutes at 4C˚,then the serum was kept at -20°C (Qauenkamp Super Cold 85) until biochemically assayed. Serum concentrations of testosterone, estrogen, progesterone, and AMH in all rats were measured using kits manufactured by Roche Diagnostics on a Cobas 6000 instrument at Bio Lab Private Laboratory, Doctor's Street, Erbil. The analyze principle of estimated hormones is chains an enzyme immunoassay competition method with a final fluorescent detection (Roche Diagnostics GmbH, Germany/Switzerland). At the end, the serum hormone concentration outcomes were automatically calculated in relation to the calibration curve and the results were expressed by ng/ml.

2.9. Data Analysis

The obtained data were conveyed as mean ± standard deviation (SD) and statistical analyses were done using the statistically available software of GraphPad Prism 9. Tukey for post hoc

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multiple comparisons and one-way analysis of variance (ANOVA) were laboring to compare means for statistical significance.

3. RESULTS

3.1. Body Weight Gain

In the existing investigation, letrozole treatment statistically significantly gained weight ($p<0.01$) after 21 days of the treatment in comparison to the control, and extremely significantly elevated ($p<0.0001$) in comparison to the flaxseed and mixed (letrozole + flaxseeds) groups. On the other hand, flaxseed extract in the mixed group caused body weight loss when in contrast to both the control ($p<0.01$) and letrozole ($p<0.0001$) groups (Fig. 1).

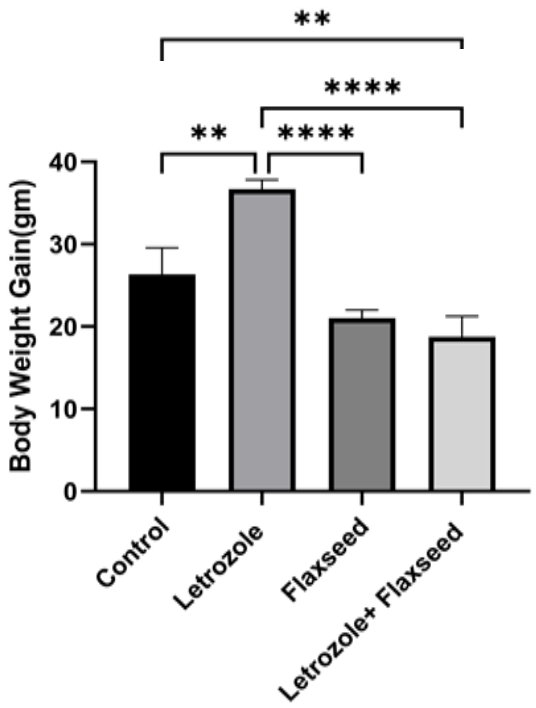

Fig. 1: Changes in body weight gain in the control, letrozole, flaxseed and letrozole+flaxseed treated rats. A difference among groups is significant: ** $p < 0.01$ and **** $p < 0.0001$

3.2. Histological Analysis

For histological analysis of ovaries in all four groups routine histological H & E was used for staining. Histopathological results of ovaries in the group of control rats displayed normal follicles containing oocytes at different maturity phases (Fig. 2). While , letrozole-induced PCOS

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group sections demonstrated severe histological variations in the ovarian histological features such as many cysts with a variable shape and size and a granulosa layer that is either very thin or absent as well as atretic follicles without oocytes. Corpora lutea were decreased or absent indicative of anovulation. In addition, they were convoyed with atretic follicles containing fluid filled antrum and congestion of the blood capillaries was frequently detected in letrozole group (Fig. 3). Histological sections from 100 mg/kg dose flaxseed group displayed normal and healthy follicles in different stages, corpora lutea and no cysts detected (Fig. 4). The combined the group (flaxseed extract and letrozole) presented a high likeness in the common histological feature of the ovary compared to the control and flaxseed treated groups. When compared to the control and flaxseed-treated groups, the combined group (letrozole plus flaxseed extract) showed a significant degree of similarity in the common histological characteristic of the ovary. Also many corpora lutea and graafian follicles with obviously distinguished oocytes, granulosa cell layers, corona radiate, cumulus oophorus and thecal cells were detected (Fig. 5).

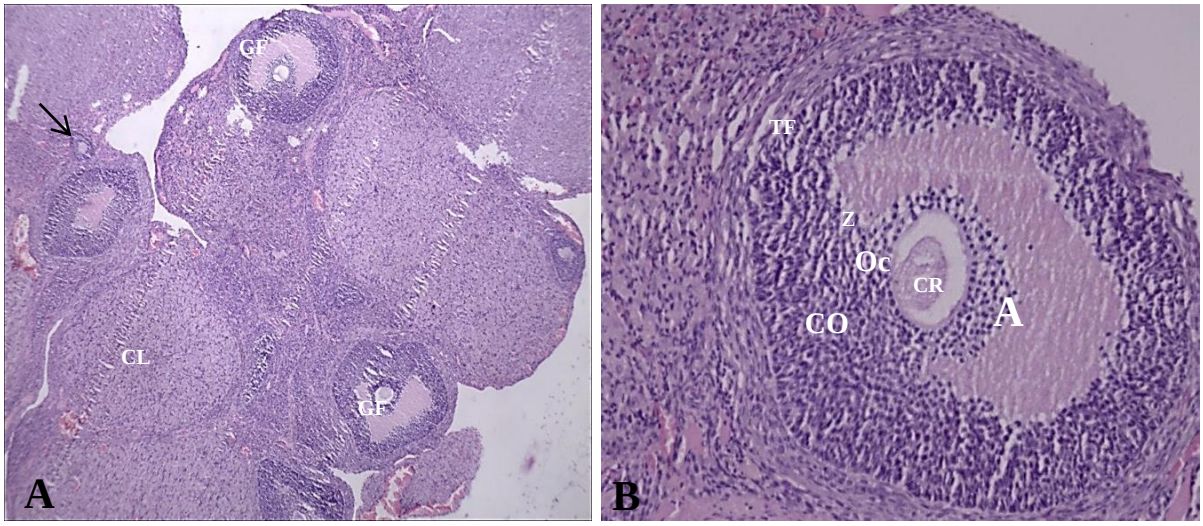

Fig. 2: Photomicrographs of the rat ovary from the control group showing: A) Follicles at various stages with normal follicle primary follicle (arrow), graafian follicle has oocyte(GF) as well as corpus luteum (CL), H&E, 40x. B) Graafian follicle has a large fluid-filled antrum (A), large oocyte (Oc) was surrounded by zona pollucida (Z), corona radiata (CR), cumulus oophorus (CO) connected the oocyte to the follicle and theca folliculi (TF), H&E, 100x.

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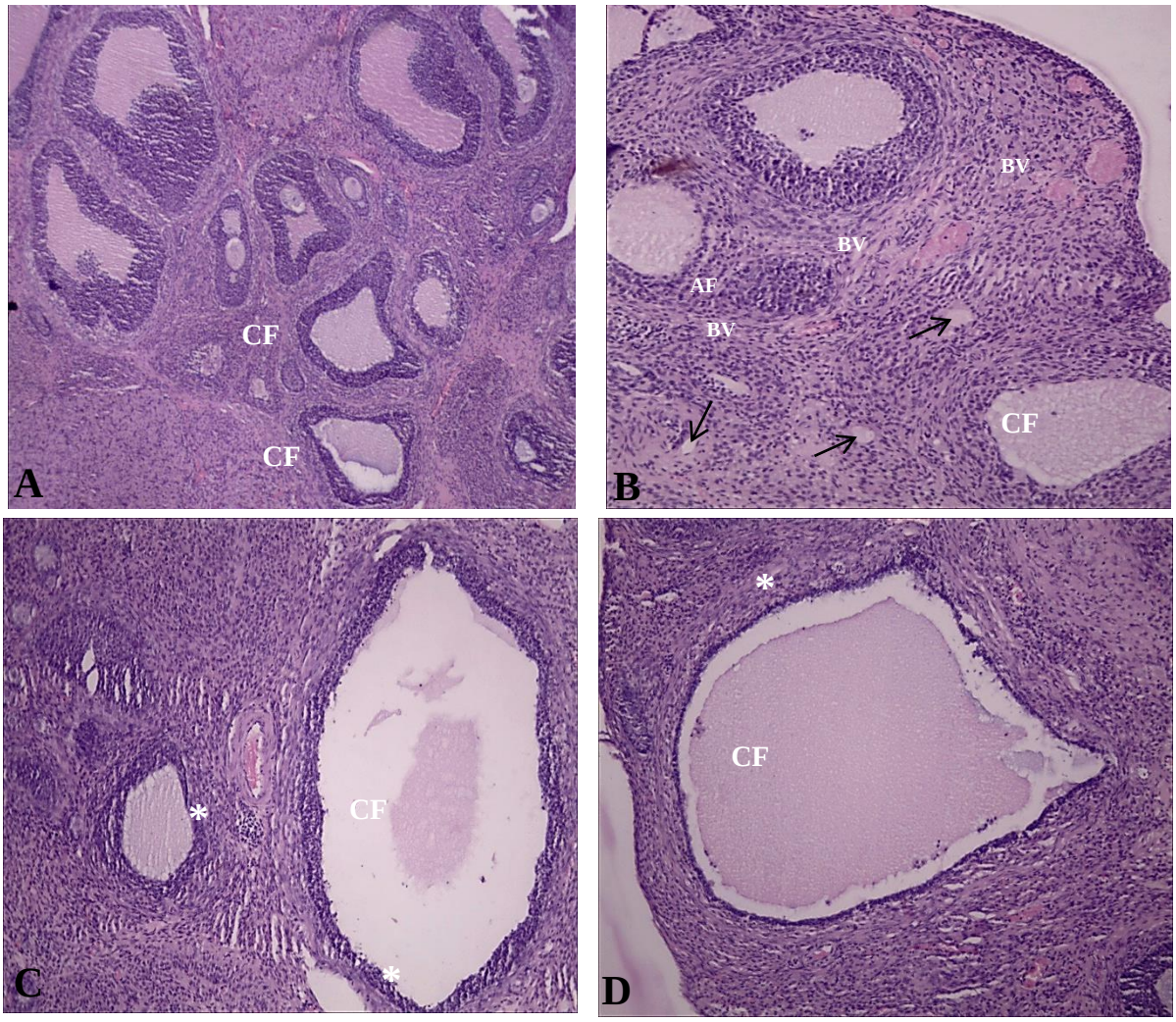

Fig. 3: Photomicrographs of the rat ovary from the letrozole-induced PCO group: A) Numerous subcapsular follicular cysts (CF) with the disappearance of oocytes, H&E, 40x. B) Dilated congested blood vessels (BV) and vacuolated interstitial cells (arrows) within the ovarian medulla and degenerated atretic follicles (AF) were also evident, H&E, 100x. C&D) Larger cystic follicles (CF) with thin-walled and degenerated oocyte (star), H&E, 100x.

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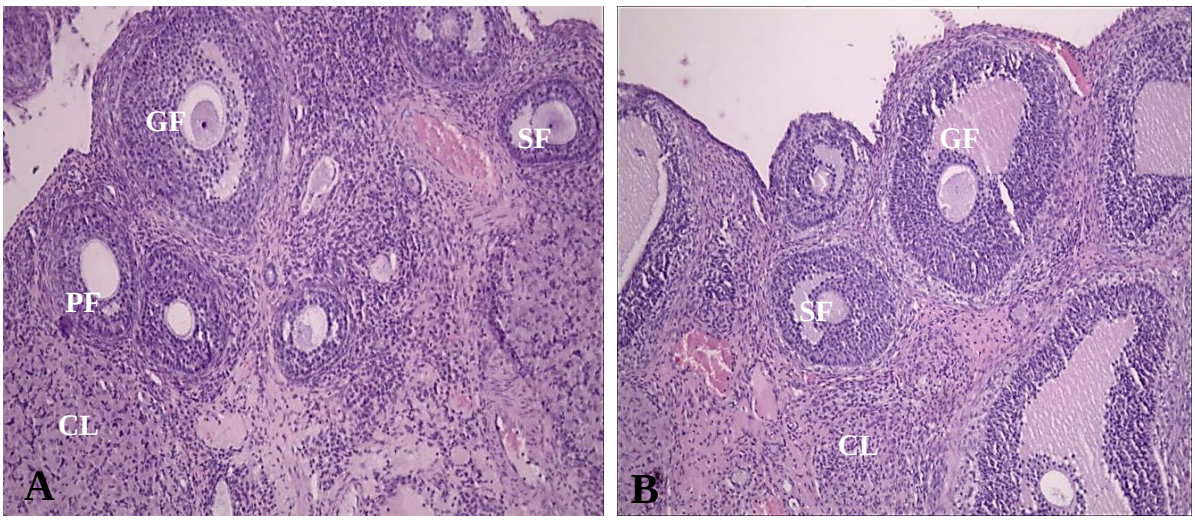

Fig.4: Photomicrographs of the rat ovary from the flaxseed-treated group showing normal and health appearance of ovarian follicles in different stages, multilaminar primary follicle (PF), secondary follicle (SF), graafian follicle(GF) and corpus luteum (CL). A&B) H&E, 100x

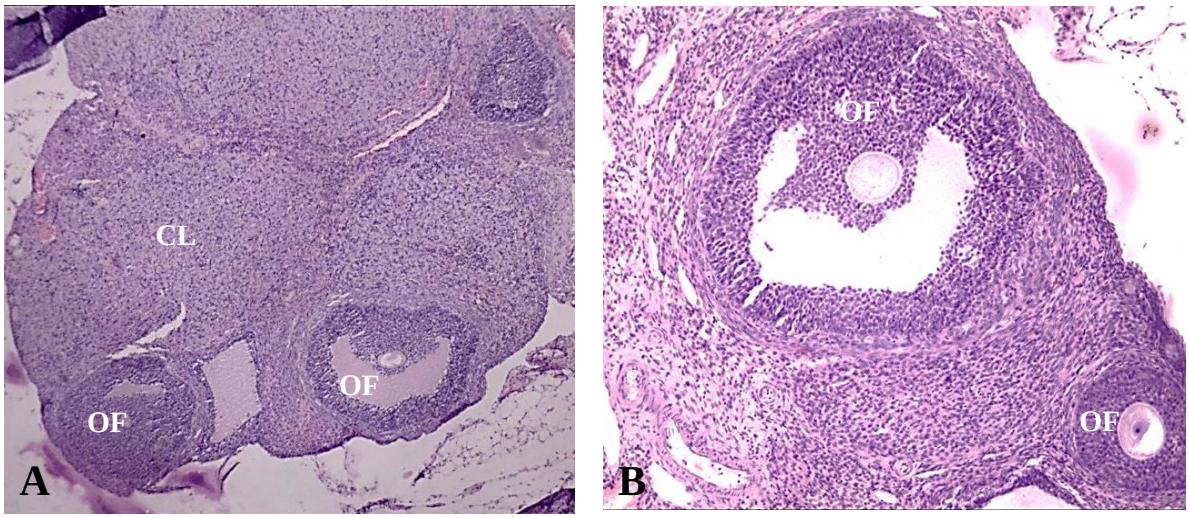

Fig.5: Photomicrographs of the rat ovary from the combined flaxseed and letrozole group illustrated normal histological architectures of ovarian follicles with oocytes (OF) and corpora lutea (CL) were found. A) H&E, 40x. B) H&E, 100x.

3.3. Hormones Assay

Concerning the sex hormones in the serum, the letrozole was caused a significant decline in the altitudes of progesterone and a non-statistically diminution in the level of estradiol hormone, while a rise in testosterone and AMH level was detected in PCOS encouraged rats by letrozole

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when compared to control However, usage with flaxseed extract optimized these values, which are presented in Table 1.

Table (1): Testosterone, estradiol, progesterone and AMH levels in rats of different groups

Studied groups / Parameters	Control	Letrozole	Flaxseed	Letrozole+Flaxseed
Testosterone	0.10±.03 ^{b****}	0.55±0.09	0.12±0.4^{b****}	0.42±0.1^{a****}
Estradiol	6.565±1.462	5.448±0.614	8.753±0.875^{b**}	6.650±1.537
Progestrone	9.133±1.9	4.450±1.1^{a*}	7.667±1.9	7.540±1.5
AMH	1.730±0.3	2.553±0.1^{a*}	1.495±0.2^{b**}	2.633±0.4

One-way ANOVA followed by post hoc Tukey's comparative statistical analysis. All results were expressed as mean ± SD; SD: standard deviation, ^{a} significant versus control group and ^{b} significant versus letrozole group. AMH stands for anti-Mullerian hormone. A difference among groups is significant: * $p < 0.05$, ** $p < 0.01$ and **** $p < 0.0001$

4. DISCUSSION

In the existing work, there was a detected surge in body weight in the PCOS group rats. So, this change has been confirmed by some studies, which have revealed a positive relationship between letrozole and body weight gain, some of them reported that letrozloe declined immunoexpression of the insulin receptor led to increased body weight [18, 19]. The metabolic abnormalities in PCOS may be because of hormonal imbalance, more so high concentrations of testosterone, leading to pancreatic ß cell dysfunction and insulin resistance. So, these physiological malfunctions resulted in weight gain due to letrozole [15]. Rezvanfar, et al. [20] and Padmanabhan and Veiga-Lopez [21] recognized that letrozole usage has a direct link with bodyweight which is a key feature of PCOS including obesity, altered glucose tolerance, hyperandrogenism and cystic follicle formation was encouraged, representing the successful founding of our model.

Rats treated with letrozole exhibited classic PCOS features like the presence of several cysts, this finding is indicative of anovulation and arrested follicular growth and is in accordance with the study by [22], which established that letrozole-induced PCOS models exhibit ovarian cyst formation and a decrease in corpora lutea. Besides, the reduced number of granulosa cell layers

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around cystic follicles in the letrozole group is consistent with the observation of Mohamed Abd El-Galil and Fathy Mohammed [15], where they observed thinning of granulosa cells in letrozole-induced cystic ovaries. Degeneration of granulosa cells is a typical hallmark of follicular atresia and is usually associated with oxidative stress and disrupted follicular development in PCOS models [14]. Remedy with flaxseed extract exhibited potential regenerative effects on ovarian morphology, the regression of cysts and the presence of follicles at different stages of development, including corpora lutea, indicate the resumption of normal ovulatory function and folliculogenesis [5]. These results are also supported by previous studies, where flaxseed extract was found to induce follicular development and growth like increasing the number of graafian follicles, and reduce cystic follicles [23]. The lignans and phytoestrogens in flaxseed are suspected to modulate estrogenic activity, improve ovarian steroidogenesis, reduce androgen excess and thereby normalize follicular development [24]. Moreover, flaxseed extraction using has the ability to reverse letrozole-induced ovarian aberrations [25]. Such synergistic effects have also been noted in other research examining the use of natural products together with conventional treatments for PCOS [26]. In the end, the results of this study show that PCOS can benefit from using flaxseed either by itself or in conjunction with letrozole. Flaxseed has the potential to be used as a natural treatment for PCOS because it normalizes follicle development, encourages ovulation, and decreases cyst formation [27].

Morgante, et al. [28] and Le, et al. [29] reported that letrozole administration significantly reduces estradiol and progesterone and elevates in testosterone and AMH levels. These findings point towards the inhibition of aromatase by letrozole, which inhibits the conversion of androgens to estrogens [30], leading to hyperandrogenism and ovarian dysfunction [31]. The higher levels of AMH described in this model are compatible with the higher number of immature follicles characteristically present in PCOS [32, 33]. Usage with flaxseed extract decreased testosterone levels while the levels of estradiol and progesterone partially recovered [13]. This suggests that phytoestrogenic compounds in flaxseed particularly lignans, may ameliorate hyperandrogenism and help achieve balance of the hormones [15]. Combining flaxseed with letrozole therapy provided additional improvement in these hormonal variables, with the evidence pointing toward a possible synergistic effect [27].

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5. CONCLUSION

The findings of the existing work indicated that letrozole prompted PCOS in rats, leading to increased body weight, development of ovarian cysts, and hormonal imbalance. However, treatment with flaxseed extract reduced the symptoms by restoring ovarian histology, reducing cysts, enhancing follicular growth, and normalizing hormone levels. These effects are likely attributed to flaxseed phytochemicals, antioxidants, and anti-inflammatory activities.

Limitations of this Study

Although this research is useful in offering information concerning the letrozole effect on the ovary and the protective effect of flaxseed, it is significant to note that this research has a number of limitations. The nature of the present study is limited as it used a small sample size and the study was performed within a limited time. Moreover, the underlying molecular mechanisms through which flaxseed exerts its effects on ovarian function remain inadequately explored. Investigating gene expression profiles and related signaling pathways could provide deeper insights into the molecular events involved in follicular development, cyst reduction, and tissue repair.

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Conflict of interests

Authors declare that they don't have any conflict of interests.

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الخلاصة

المقدمة: متلازمة تكيس المبايض (PCOS) هي حالة أيضية تؤثر على الإناث خلال سنوات الإنجاب. تتميز متلازمة تكيس المبايض بوجود بصيلات متعددة تشبه الأكياس على المبايض، وعدم انتظام أو غياب التبويض، ومقاومة الأنسولين. يهدف هذا البحث إلى دراسة آثار مستخلص بذور الكتان على المبيض في جرذان مصابة بمتلازمة تكيس المبايض، وذلك من خلال التقنيات النسيجية ومستوى الهرمونات في المصل.

طرق العمل: تم توزيع ستة عشر من إناث الفئران البيضاء (عمرها من 6 إلى 8 أسابيع، دورة الشبق لدى إناث الفئران تتكرر كل 4 إلى 5 أيام) إلى أربع مجموعات: المجموعة الأولى هي المجموعة السيطرة، المجموعة الثانية تلقت 0.2 ملغ / كجم من وزن الجسم من الليتروزول عن طريق التجريع الفمي , المجموعة الثالثة أعطيت 100 ملغ / كجم من وزن الجسم من مستخلص بذور الكتان عن طريق الحقن، والمجموعة المختلطة تلقت كل من الليتروزول وبذور الكتان يوميًا لمدة 21 يومًا.

النتائج: أظهر الفحص النسيجي للمبيض وجود كيس مبيضي ناتج عن الليتروزول وتمزق الجريبات. أدى العلاج ببذور الكتان إلى استعادة شكل المبيض بشكل ملحوظ، مع استعادة نمو الجريبات. أشار التحليل الهرموني إلى ارتفاع مستوى هرمون التستوستيرون وهرمون Anti–Müllerian Hormone، بينما انخفض مستوى هرموني الإستروجين والبروجسترون في مجموعة الليتروزول مقارنةً بالمجموعات الأخرى. أعاد استخلاص مكملات بذور الكتان التوازن الهرموني، مما أدى إلى انخفاض مستوى التستوستيرون وزيادة مستوى الإستروجين والبروجسترون.

الاستنتاجات: تُظهر هذه النتائج أن مستخلص بذور الكتان قد يُقدّم خيارًا علاجيًا فعالًا لمتلازمة تكيس المبايض من خلال تعديل اختلالات المبيض والهرمونات.

الكلمات المفتاحية: تكيسات المبيض، بذور الكتان، متلازمة تكيس المبايض، ليتروزول، مضاد للأكسدة اناث، جرذ البينو، دراسة نسيجية