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Ameliorative effect of hydroalcoholic *Cinnamon zeylanicum* extract against oxidative stress in a rat model of Letrozole-induced polycystic ovary syndrome

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ABSTRACT

Polycystic Ovary Syndrome (PCOS) is one of the most frequent conditions, which affects both metabolic and reproductive systems causing irregular menstrual cycles, chronic anovulation, and hyper-androgenism. The beneficial effects of Cinnamon zeylanicum (CZ) Hydroalcoholic extract on oxidative injury and hormonal alterations in adult rats with PCOS were evaluated. PCOS was induced by administration of letrozole (1mg/kg b. wt. /day, orally) for 4 weeks. Four weeks after PCOS induction, treatment with Metformin (150mg/kg b. wt./day) and Cinnamon zeylanicum (CZ) Hydroalcoholic extract (200mg/kg b. wt./day), orally were started and continued for 30 days. Fifty female rats were equally divided into 5 groups. Group I (Normal control):Rats received no drugs, Group II (letrozole-induced PCOS): Rats were orally administrated 1mg/kg b. wt. /day of letrozole for 4 weeks, Group III (Metformin treated): After 4 weeks of letrozole administration, rats were orally treated with 150mg/kg b. wt./day of metformin for 30 days, Group IV (CZ treated): Rats were administrated letrozole as group II and orally treated with 200mg/kg b. wt./day of Hydroalcoholic extract of CZ for 30 days, Group V (metformin + CZ treated): Rats were administrated letrozole and treated daily with metformin and CZ for 30 days as group III+IV. The results revealed a significant decrease in serum estrogen, progesterone and antioxidant markers with marked elevations in serum MDA, total cholesterol and triacylglycerol concentrations in PCOS as compared with normal control group. However, treatment with Hydroalcoholic extract of CZ or/and Metformin to PCOS rats caused remarkable ameliorations in all previous parameters. Conclusively, the Hydroalcoholic extract of CZ treatment ameliorates oxidative injury caused by letrozole enhances the antioxidant defense system, and prevents lipid peroxidation.

1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is a metabolic and endocrine disorder that affects 6–14% of women of reproductive age. PCOS women have higher rates of obesity, insulin insufficiency, diabetes mellitus risk, and cardiovascular illness. According to some studies, obesity and oxidative injury may be significant contributors to infertility and other diverse illnesses that are prevalent in individuals suffering from PCOS (Rojas et al., 2014). It is distinguished by the morphology of polycystic ovaries, Hyperandrogenism, hirsutism, irregular menstruation, malfunction of the ovaries, and infertility (Rostamtabar et al., 2021). Oxidative injury is an unbalanced ratio of antioxidants to oxidants in living cells. Multiple investigations exhibited that oxidative injury is typically prevalent in PCOS-affected females, regardless of whether they are thin or have metabolic abnormalities (Sabuncu et al., 2001). New studies strongly suggest that insulin insufficiency is crucial to polycystic ovarian syndrome's etiology and that it increases oxidative injury, even though the basic mechanisms for oxidative injury in PCOS are not fully known.

According to Murri et al. (2013), insulin insufficiency may result from oxidative injury, which is brought on by free radicals, highly toxic chemicals development like malondialdehyde (MDA), and other lipid peroxidation final products. *Cinnamomum zeylanicum* is a member of the Lauraceae family and an herbaceous plant. It is considered the most important spice consumed by humans around the world. Since it has been used for digestive, gynecological, and respiratory disorders since earliest records, *Cinnamomum zeylanicum*, also known as cinnamon, sometimes known as CZ, is a pharmaceutical natural plant with a variety of curative characteristics (Kaewpiboon et al., 2012). Current theories on how cinnamon acts as a medicine attribute these outcomes to the presence of bioactive components like polyphenolic compounds. Cinnamaldehyde, the primary active ingredient of *Cinnamomum zeylanicum*, provides a number of health advantages, including antioxidant, antidiabetic, antibacterial, anti-inflammatory, and stomach ulcer prevention properties (Dorri et al., 2018). This study aimed to investigate the possible impact of Hydroalcoholic *Cinnamomum zeylanicum* extract on improving oxidative injury and, dyslipidemia in a rat model of letrozole-induced PCOS.

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2. MATERIAL AND METHODS

2.1. Drugs

Letrozole (Femara®): chemical drug of Novartis, Istanbul, Turkey, acts as an aromatase inhibitor. It exists in the form of film-coated tablets, each one containing 2.5 mg letrozole which is freshly dissolved in distilled water, and, given orally at a dose of (1 mg/kg. B.wt./day)for 4 weeks, (Feyzollahi et al., 2021). Metformin (Glucophage®): Metformin was commercially available as Glucophage from Merck Santé, Germany, and exists in the form of a film-coated tablets, each one tablet contains 1000 mg. Tablets were dissolved in 0.9% saline water as a vehicle, and freshly administered orally at a dose of (150 mg/kg. b.wt/day) for 30 days,(ul haq Shah et al., 2022)

2.2. Cinnamon zeylanicum

2.2.1 Preparation of Hydroalcoholic Cinnamon zeylanicum extract:

About0.5 kg of *Cinnamon zeylanicum* plant bark were used for CZ extract Preparation. To produce liquid extract, the plant was first ground into a powder, then dissolved in 70% ethanol and maintained on the Thermo Fisher's shaker for 48 hours at the room temperature. The created solution was then filtered by filter paper into flask, centrifuged at 3000 rpm for five minutes, infused into an open dish. Finally, the produced extract was dissolved in ordinary distilled water for the desired concentration(Khodaeifar et al., 2019b).

2.3. Animals

Fifty adult Wister albino female rats of 3 months old and weighing 200-250 g average weight were obtained from the National Research Center (Giza, Egypt). They were kept in separated cages with favorable climatic and dietary circumstances throughout the experiment. They were acclimatized for 2 weeks before starting the experiment. The Experimental protocol was conducted according to the guide for Institutional Animals Care and Use Committee approved by Research Ethics Board, Faculty of Veterinary Medicine, Benha University. (Approval no. BUFVTM 23-02-23).

2.4. Experimental design

Rats were equally divided into 5 groups (10 each). They were placed in individual cages and, classified as follows:
Group I (Normal control): Rats received normal diet without medications. Group II (letrozole-induced PCOS): Rats administered letrozole (1mg/kg b. wt. /day, orally) for 4 weeks. Group III (Metformin treated): Four weeks after PCOS induction rats treated with metformin (150mg/kg b. wt./day), orally and continued for 30 days. Group IV (CZ treated):Four weeks after PCOS induction rats administered with Cinnamon zeylanicum (CZ) Hydroalcoholic extract at a dose of (200mg/kg b. wt./day) orally and continued for 30 days.(Khodaeifar et al., 2019b). Group V (metformin + CZ treated): Rats were received letrozole (1mg/kg b. wt. /day, orally) for 4 weeks, then administered daily with metformin and CZ as group III and group IV for 30 days.

2.5. sampling

At the end of experiment (58 days) and after overnight fasting blood samples for serum separation were collected from the retro-orbital plexus from all animal groups. The blood was drawn into dry, plain test tubes and left for 0.5 hr. at room temperature, then centrifuged at 4000 rpm for 15 minutes. lastly, serum was collected by using automatic micropipettes into the Eppendorf tubes and preserved at -20℃ until used for the biochemical analysis.

2.6. Biochemical analysis

Serum estrogen and progesterone levels were determined using ELISA Kits according to Abelson et al. (2016). Also, serum total cholesterol and triacylglycerol (TG) concentrations were determined enzymatically using mercantile kits according to the method described by (Richmond, 1973) and (Bahramikia and Yazdanparast, 2008), respectively. Moreover, serum L-malondialdehyde (L-MDA) and reduced glutathione (GSH) concentrations, super oxide dismutase (SOD) and catalase(CAT) activities were determined according to the methods described by (Ohkawa et al., 1979), (Yoshioka et al. 1979),(Weydert and Cullen,2010) and (Soltani et al. (2017), respectively

2.7. Statistical analyses

To determine the variations in variable means between the groups, One-way analysis of variance (ANOVA) was used. The findings, which were displayed as the mean SE, were examined using the statistical analysis software SPSS V20. The probability has been identified as significant with a P value of 0.05.

3. RESULTS

The presented data in (Table 1) shows that, serum estrogen and Progesterone levels in PCOS- induced rats were significantly decreased when compared to the normal control group. While administration of Hydroalcoholic extract of CZ or/and metformin to POCS-induced rats provided a more marked increase in serum estrogen and progesterone concentrations as compared with PCOS non-treated rats

Table (1): Effect of Hydroalcoholic extract of CZ or/and metformin treatment on serum Estrogen and Progesterone concentrations in letrozole -induced PCOS in rats

Animal groups	Parameters	
	Estrogen (pg/ml)	progesterone (ng/ml)
GI: Normal Control	83.70±2.72^{a}	0.35±0.04^{d}
GII: PCOS	43.77±0.91^{c}	0.17±0.01^{d}
GIII: PCOS + Metformin treated	69.83±3.90^{b}	1.14±0.02^{c}
GIV: PCOS + Hydroalcoholic extract of CZ treated	74.00±1.53^{b}	3.78±0.17^{b}
GV: PCOS + Metformin + Hydroalcoholic extract of CZ treated	77.67±4.06^{ab}	7.47±0.32^{a}

Data are presented as (Mean ± SE). SE = Standard error. Mean values with different superscript letters in the same column are significantly different at ($P \leq 0.05$)

The obtained results presented in (Table 2) exhibit marked increase in serum total cholesterol and triacylglycerol concentrations in PCOS-induced rats as compared to the normal control group. Conversely, treatment with Hydroalcoholic extract of CZ or/and metformin showed obvious decrease in serum total cholesterol and triacylglycerol concentration in comparison with PCOS non treated rats

Table (2): Effect of Hydroalcoholic extract of CZ or/and metformin treatment on the serum total cholesterol and triacylglycerol concentrations in letrozole -induced PCOS in rats

Animal groups	Parameters	
	T. cholesterol (mg/dl)	Triacylglycerol (mg/dl)
GI: Normal Control	63.00±1.15^{c}	91.00±3.51^{b}
GII: PCOS	89.33±0.88^{a}	154.33±2.40^{a}
GIII: PCOS + Metformin treated	77.00±1.15^{b}	98.00±1.15b
GIV: PCOS + Hydroalcoholic extract of CZ treated	47.67±7.75^{d}	75.67±2.96^{c}
GV: PCOS + Metformin + Hydroalcoholic extract of CZ treated	63.67±2.91^{c}	63.67±1.86^{d}

Data are presented as (Mean ± SE). SE = Standard error. Mean values with different superscript letters in the same column are significantly different at ($P \leq 0.05$)

The results demonstrated in (Table 3) revealed that in PCOS-induced rat's serum MDA concentration was markedly increased, while serum GSH level, SOD and catalase activities were significantly decreased when compared with

normal control group. On the other hand, treatment of PCOS-induced rats with the Hydroalcoholic extract of CZ or /and metformin exhibited a significant decrease in serum MDA concentration with marked increase in serum GSH level, SOD and catalase activities in comparison with PCOS non-treated rats.

Table (3): Effect of Hydroalcoholic extract of CZ or/and metformin treatment on the serum MDA, GSH concentrations, SOD and catalase activities in letrozole -induced PCOS in rats

	Parameters			
	MDA (nmol/ml)	GSH (mg/dl)	SOD (U/ml)	Catalase (U/ml)
GI	20.44±0.32^{c}	29.55±0.70^{a}	17.06±0.54^{a}	5.12±0.08^{a}
GII	68.61±4.26^{a}	12.54±0.45^{d}	6.88±0.20^{e}	1.15±0.04^{d}
GIII	40.67±5.01^{b}	13.93±1.12^{d}	8.83±0.34^{d}	3.05±0.41^{b}
GIV	36.78±2.05^{b}	20.40±0.33^{c}	11.63±0.23^{c}	2.29±0.03^{c}
GV	39.42±0.32^{b}	24.73±1.38^{b}	13.80±0.47^{b}	2.96±0.10^{b}

Data are presented as (Mean ± SE). SE = Standard error. Mean values with different superscript letters in the same column are significantly different at ($P \leq 0.05$). GI: Normal Control, GII: PCOS, GIII: PCOS + Metformin treated, GIV: PCOS + Hydroalcoholic extract of CZ treated, GV: PCOS + Metformin + Hydroalcoholic extract of CZ treated

4. DISCUSSION

Since earliest times, PCOS has been treated with natural herbal medications that include cinnamon. Therefore, this research examines how the hydroalcoholic extract of *Cinnamon zeylanicumcan* be utilized to regulate specific sex hormonesfunction as an agent toco mbat high levels of lipids in the blood, and exhibit strong a ntioxidant properties. A marked decrease in the serum Estrogen and Progesterone concentrations was observed in PCOS-induced animals. These results agree well with data reported by Kafali et al. (2004) who found that letrozole administration caused a significant reduction in serum Estrogen and Progesterone concentrations when compared with the control. This result may be due to that Letrozole is a P450 aromatase enzyme inhibitor that prevents the enzyme from converting testosterone and androstenedione into estrone and estradiol during the steroidogenesis process. Estradiol is created by the granulosa cell-produced aromatase converting C19 androgens. Letrozole may reduce the activity of the aromatase enzyme, which may lead to higher ovarian androgen levels, a decrease in estrogen, and the onset of PCOS (Mills et al., 2014).Nevertheless, treatment with *C. zeylanicum* can increase Estrogen levels in the plasma, while decreasing testosterone and gonadotropin levels in the blood. The natural plants have the power of antioxidant characteristics ,can lower serum gonadotropin and insulin levels in the serum according to the earlier studies in PCOS populations(Costello et al., 2016).On the one hand, the results of a different study showed that a drop in plasma estrogen levels in the PCOS group is likely linked to a decrease plasma aromatase levels in that group(Cook et al., 2002). A marked increase in serum total cholesterol and triacylglycerol concentrations were observed in letrozole – induced PCOS in rats. Similarly, Ibrahim et al. (2020) who found that letrozole caused a marked increase in the serum lipid profile more than the normal animals. Dyslipidemia, or lower HDL-C and higher plasma total lipid, total cholesterol, and triacylglycerol levels is one of the side effects of PCOS (Hung et al., 2014). Hyperandrogenism is the cause of abnormalities in the lipid profile. (Croston et al., 1997). Administration of Hydroalcoholic extract of *Cinnamon zeylanicum* or/and metformin to diseased rats had a significant negative impact on the earlier findings because C. zeylanicum extracts had a significant positive impact on the regulation of plasma lipid profile levels, including a decrease in serum levels of LDL, TG, and cholesterol and an increase in the level of HDL. The extract of C. zeylanicum may also reduce hyperlipidemia and raise HDL levels(Tuzcu et al., 2017). The results of existing study revealed that in PCOS-induced rat's serum MDA concentration was markedly increased, while serum GSH level, SOD and catalase activities were significantly decreased when compared with normal control group. These results agree with Bal et al. (2023)who proved that PCOS rats showed marked alterations between oxidant and anti-oxidant systems causing cellular oxidative stress. This effect might be caused by the insufficiency of antioxidant markers particularly GSH concentration, SOD, and CAT activities causes the massive ROS (reactive oxygen species) generation, which affects ovulation, folliculogenesis, and oocyte maturation are all physiological processes that occur in the ovary(Lu et al., 2018). The catalase levels which can detoxify H_2O_2 to water, and maintain the growth of follicles and ovarian function (Sun et al., 2019). The drop in GSH concentrations, augmented oxygen radicals(ROS)are observed in PCOS patients(Dona et al., 2012). Earlier research indicates that PCOS undergo oxidative damage, as evidenced by a decrease in endogenous antioxidants such as GSH, SOD, and CAT. However, the administration of cinnamon zeylanicum therapy effectively restored these antioxidant levels in PCOS rats, demonstrating the antioxidative properties of cinnamon zeylanicum. Cinnamon possesses antioxidants characteristics that can prevent the activity of oxygen species and reduce oxidative damage. Thus, when the Hydroalcoholic extract of cinnamon zeylanicum and/or metformin were administered to diseased rats, the detrimental effects were significantly prevented. Furthermore, the cinnamon zeylanicum extract may also contribute to lowering insulin and fasting blood sugar levels in the plasma. Its antioxidant combination, which includes resin, tannin, aldehyde transcine, linalool, coumarin, and limonene, can help alleviate insulin insufficiency (Khodaeifar et al., 2019a).

5. CONCLUSIONS

The current study could be concluded that the administration of Hydroalcoholic extract of *Cinnamon zeylanicum* and/or metformin (Glucophage®) drug to letrozole-induced PCOS provided a reliable therapeutic choice for oxidative injury, dyslipidemia, and hormonal imbalance; since, these natural herbs can improve the alterations of the ovary, and may play a special role in treating PCOS. So, we recommend the use of Hydroalcoholic extract of *Cinnamon zeylanicum* for the treatment of PCOS.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest for current data

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