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Selected Toxicity Study on Ethanolic Extract of *Ocimum* gratissimum (Linn.) Leaves in Letrozole-Induced Polycystic Ovarian Syndrome in Wistar Rats

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ABSTRACT

Polycystic Ovarian Syndrome (PCOS) is a metabolic endocrine disorder that is common in women of reproductive age. Several synthetic drugs such as metformin are treatment options of PCOS but the side effects associated with the use of metformin have continued to limit their acceptability; Thus, necessitate the investigation of the safety of Ocimum gratissimum leaves in vivo. The toxicity of ethanolic extract of Ocimum gratissimum leaf (EEOGL) at 50 and 100mg/kg body weight dosage on PCOS was investigated in female Wistar rats. Twenty female Wistar rats with an average weight of 170.81±5.25g were allocated into 5 groups (A-E) of four animals each: group A animals (control) received distilled water while the letrozole-induced (1mg/kg body weight (B.Wt)) rats- groups B, C, D, and We were administered distilled water, co-administration of 7.14mg/kg B.Wt of metformin and 2mg/kg B.Wt of clomiphene citrate, 50mg/kg and 100mg/kg of EEOGL for 21 days respectively. The liver and kidney function indices were determined after each rat was sacrificed and blood collected by jugular puncturing. The data collected were subjected to analysis of variance and Duncan multiple range test with statistical significance set at p < 0.05. The result reveals a significant increase (p < 0.05) and a significant decrease (p<0.05) at doses of 50mg/kg and 100mg/kg of EEOGL on kidney function indices as well as liver function indices respectively. Therefore, the administration of EEOGL at 50 and 100 mg/kg B.W. to letrozole-induced PCOS rats shows mild alterations in the assayed toxicological indices.

Keywords: Letrozole, Polycystic Ovarian Syndrome, Toxicity, EEOGL.

INTRODUCTION

The oestrogens and progestogens are the major reproductive hormones in females, that act through the Plants have been inherited as a source of medication and are an important part of the health care system. Plants contain valuable information in the form of medicinal knowledge that has been preserved for the sake of modern health care system ^[1]. Plants that are known to possess therapeutic properties due to several investigations, studies and research are commonly known as "Medicinal plants". Plants used in traditional medicine provide a wide variety of drug and can be used for the treatment of both chronic and infectious diseases ^[1]. Therefore, special focus should be given to the genetic makeup, physiology, morphology of the species to extract its potential as therapeutic value. A good example of this medicinal plant is *Ocimum gratissimum*.

Ocimum gratissimum, also known as clove basil or lemon basil but popularly known as "scent leaf" has been reported to be a culinary herb with wide therapeutic applications ^[1]. *Ocimum gratissimum* is a medicinal plant that is mainly distributed in tropical regions and native to South Asia, Africa, and various regions of South America. It has been used as local condiment and dental care product in Nigeria and other parts of the world. Also, *Ocimum gratissimum* had been reported to as have medicinal properties hence its use in local or alternative medicine ^[2]. It has antimicrobial, antidiabetic, antidiarrheal, insecticidal, and anti-cancerous potential/properties ^[1].

Polycystic Ovarian Syndrome (PCOS) or Stein- Leventhal syndrome is a metabolic endocrine disorder that is very common in women of reproductive age affecting approximately 2-10% of them ^[3]. It has several consequences in female health including alarming rate of infertility ^[4]. PCOS is a complex gynaecological condition that is often indicated by the presence of at least two of the three stated criteria: hyperandrogenism, ovulatory dysfunction, and polycystic ovaries ^[5].

This metabolic disorder is caused by several hormonal imbalances, detected through clinical manifestations, of which hyperandrogenism and chronic anovulation are dominant which can cause either a long-term or short-term effect on female health care ^[3]. Hormonal disturbances associated with

PCOS includes insulin resistance and hyperinsulinemia.

Women suffering from this disease tend to have an increased prevalence of several other metabolic diseases of which include type 2 diabetes mellitus, dyslipidemia, metabolic syndrome, and obesity ^[6]. Amongst the comorbidities mentioned, obesity has been investigated to be at an epidemic climax with a worldwide rife of 35% in female ^[7]. Due to a series of studies and research, it has been investigated that insulin resistance (IR) has a fundamental link associated with these conditions ^[8]. Although insulin resistance may be present in PCOS patients free of obesity ^[9]. Due to the risks of toxicity associated with herbal products as alerted many national and international regulatory authorities to develop and implement various sets of guidelines for assessing, monitoring, and preventing the toxicity associated with such herbal products ^[10].

Toxicological evaluations are used extensively to investigate specific adverse occurrence or endpoints such as allergies, cancer, nephrotoxicity etc. Therefore, it is imperative to ascertain the safety in the usage of botanicals, such as *Ocimum gratissimum*, with fertility-enhancing activity as oral remedies in normal experimental animals and those induced with the PCOS condition in order to increase their acceptability ^[11].

MATERIAL AND METHODS

Plant Material

Fresh leaves of *Ocimum gratissimum* were purchased from Magboro market, Ogun state, Nigeria. The authentication of the plant was carried out at Department of Plant Biology, University of Lagos, Lagos, Nigeria by Mr. Nodza George. A voucher specimen number LUH 8752 was prepared and deposited at the departmental herbarium.

Animals

Twenty female albino rats with an average weight of 170.81 ± 5.25 g was obtained from the Animal Holding unit of the University of Lagos, Lagos, Nigeria. They were kept in a well-ventilated house condition and fed with standard diet (Vital feeds, grand cereals) and clean water.

Assays Kits, Chemicals and Drugs

Albumin, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, uric acid, creatinine and total protein assay kits were products of Randox laboratory, Liquizyme, United Kingdom.

Preparation of Extract

A known weight of 1,468g of *Ocimum gratissimum* leaves was washed to remove contaminants and air-dried to remove water content and attain constant weight The dried leaves was pulverized and 388g was soaked in 1,400ml of absolute ethanol for 48hours. The extract was sieved with a jute bag into a plastic container and filtered using Whatman's No. 1 filter paper. The filtrate was lyophilized and a yield of 31.21g (9.23%) was obtained.

Ethical Clearance

All the animals were subjected to humane care based on the conditions stated in the 'Guide for the Care and Use of Laboratory Animals' prepared by the National Academy of Science (NAS) and published by the National Institute of Health (National Research Council, 2010). The institution approved experimental number of the Principal Investigator is 17010102012.

Animal grouping and extract administration

Twenty female waster rats of average weight of 170.81 ± 5.25 g was acclimatized for one week under standard housing conditions and fed with rat pellets and water *ad libitum*. The Wistar rats were induced when they were in their estrus stage. The animals were grouped based on similarity in body weight into five groups of four animals as follows:

Group 1 (Control group) - received only animal feed and water

Group 2 (Letrozole-induced) - received 1ml of distilled water

Group 3 (Letrozole-induced) – received 0.5ml of 7.14mg/kg body weight of metformin and 0.5ml of 2mg/kg body weight clomiphene citrate (Reference drugs)

Group 4 (Letrozole-induced) – received 0.5ml ethanolic extract of *Ocimum gratissimum* leaves

Group 5 (Letrozole-induced) – received 1ml of ethanolic extract of *Ocimum gratissimum* leaves

To those who required 0.5 ml and 1ml of the plant extract, 1ml of distilled water and 1ml of metformin + clomiphene citrate that corresponds to their respective doses were given once daily for twenty-one days using oral administration. At the end of the 21 days period, the animals were anesthetized using diethyl ether and blood was obtained via the jugular. Thereafter, the liver and kidney were isolated, homogenized and centrifuged ant supernatant was stored at - 4°C for further analysis.

Preparation of Serum and Tissue Supernatants

The weighed rats were anaesthetized in a jar containing cotton wool soaked in diethyl ether. The fur and skin in the jugular and skin were displaced to expose the jugular veins and thereafter cut with a sharp sterile blade. The animals were held head downwards, allowed to bleed into clean, dry sample tubes and left at room temperature for 10 minutes to clot. The blood samples were centrifuged at 3000rpm for 10 minutes to obtain the supernatant (serum) from the stock using Thermos Scientific Centrifuge (Heraeus Megafuge 8).

The sera were thereafter aspirated using micro flux pipette into clean, dry, sample bottles and frozen (-4°C) overnight. The animals were quickly dissected to excise the liver and kidney. These organs were cleaned of fatty layers, weighed, and transferred into ice cold 2M sucrose solution. Thereafter, each organ was blotted with blotting paper, cut thinly with a sterile blade, and homogenized separately in ice cold 0.25M sucrose solution (1:4 w/v) based on their different dilution factors used such as kidney (x60) and liver (x30). The homogenates obtained were centrifuged at 3000rpm for 10 minutes to obtain the supernatants which were collected into sample bottles and frozen (-4°C) overnight further biochemical assays ^[12].

Evaluation of Biochemical Indices

Albumin, globulin, total and conjugated bilirubin, urea, uric acid,

creatinine, ALP, AST, and ALT concentrations were determined via standard procedures ^[13].

Statistical Analysis

Data were expressed as the mean \pm standard error of mean (SEM) of four determinations and data were considered to be significant at P<0.05 using One Way Analysis of Variance and Duncan Multiple Range Test performed using Statistical Package for Social Sciences, version 26.0 (SPSS Inc., Chicago, USA).

RESULTS

The effect of EEOGL on some liver function indices of Letrozoleinduced female rats reveals that albumin concentration (table 1) increased significantly (p<0.05) in letrozole-induced PCOS in female rats orally administered distilled water, clomiphene citrate and metformin, 50mg/kg body weight (b. wt.) of the extract and 100 mg/kg b. wt. of the extract was increased significantly (p<0.05) compared to that of the control animals. The serum albumin levels of Letrozole-induced rats administered distilled water compared favorably (p>0.05).

Globulin concentration decreased significantly (p<0.05) in Letrozoleinduced rats orally administered distilled water while the globulin concentration in Letrozole-induced rats orally administered clomiphene citrate and metformin, 50mg/kg b. wt. of the extract and 100mg/kg b. wt. of the extract was increased significantly (p<0.05) compared to that of the control animals. The serum globulin levels of Letrozole-induced female rats administered distilled water compared favorably (p>0.05).

Total protein concentration decreased significantly (p<0.05) in Letrozole-induced rats orally administered clomiphene citrate and metformin while the total protein concentration in Letrozole-induced rats orally administered distilled water, 50 and 100 mg/kg b. wt. of the extract was increased significantly (p<0.05) compared to that of the control animals.

Direct bilirubin concentration decreased significantly (p<0.05) in Letrozole-induced rats orally administered distilled water, 50 100 mg/kg b. wt. of the extract while the direct bilirubin concentration increased significantly (p<0.05) in Letrozole-induced rats orally administered clomiphene citrate and metformin compared to that of the control animals.

Total bilirubin concentration increased significantly (p<0.05) in Letrozole-induced rats orally administered distilled water and 100 mg/kg b. wt. of the extract while total bilirubin concentration decreased significantly (p<0.05) in Letrozole-induced rats orally administered clomiphene citrate and metformin and 50 mg/kg b. wt. of the extract compared to that of the control animals.

Albumin-globulin ratio concentration increased significantly (p<0.05) in Letrozole-induced rats orally administered distilled water while albumin-globulin ratio concentration decreased significantly in Letrozole-induced rats orally administered clomiphene citrate and metformin, 50 and 100 mg/kg b. wt. of the extract was increased significantly (p<0.05) compared to that of the control animals.

The effect of EEOGL on some kidney function indices of Letrozoleinduced female rats reveals that creatinine concentration (table 2) increased significantly (p<0.05) in Letrozole-induced rats orally administered distilled water, clomiphene citrate and metformin, 50 mg/kg b. wt. of the extract while creatinine concentration decreased significantly (p<0.05) in Letrozole-induced rats orally administered 100 mg/kg b. wt. of the extract compared to that of the control animals. Urea concentration decreased significantly (p<0.05) in Letrozole-

induced rats orally administered distilled water while urea concentration increased significantly (p<0.05) in clomiphene citrate and metformin, 50 and 100mg/kg b. wt. of the extract compared to that of the control animals.

Uric acid concentration increased significantly (p<0.05) in Letrozoleinduced rats orally administered distilled water, clomiphene citrate and metformin, 50 and 100mg/kg b. wt. of the extract compared to that of the control animals.

Blood urea nitrogen-creatinine ratio concentration decreased significantly (p<0.05) in distilled water while blood urea nitrogencreatinine ratio concentration increased significantly (p<0.05) in clomiphene citrate and metformin, 50 and 100 mg/kg b. wt. of the extract compared to that of the control animals.

The result obtained from aspartate aminotransferase activity in the liver (Table 3) decreased significantly (p<0.05) in Letrozole-induced rats orally administered distilled water, clomiphene citrate and metformin, 50 and 100mg/kg b. wt. of the extract compared to that of the control animals.

Aspartate aminotransferase activity in the serum decreased significantly (p<0.05) in PCOS- induced rats orally administered distilled water, clomiphene citrate and metformin, 50mg/kg per body weight of the extract while aspartate aminotransferase activity in the serum increased significantly (p<0.05) in PCOS- induced rats orally administered 100mg/kg per body weight of the extract compared to that of the control animals.

The result obtained from alkaline phosphatase activity in the liver (table 4) decreased significantly (p<0.05) in Letrozole-induced rats orally administered distilled water, clomiphene citrate and metformin, 50 and 100mg/kg per b. wt. of the extract compared to that of the control animals.

Alkaline phosphatase activity in the serum increased significantly (p<0.05) in Letrozole-induced rats orally administered distilled water, clomiphene citrate and metformin, 50 and 100 mg/kg b. wt. of the extract compared to that of the control animals.

The result obtained for alanine aminotransferase activity in the serum (table 3) decreased significantly (p<0.05) in Letrozole-induced rats orally administered clomiphene citrate and metformin and 50mg/kg per body weight of the extract while alanine aminotransferase activity in the serum increased significantly (p<0.05) in Letrozole-induced rats orally administered distilled water and 100 mg/kg b. wt. of the extract compared to that of the control animals.

Alanine aminotransferase activity in the liver increased significantly (p<0.05) in Letrozole-induced rats orally administered distilled water, clomiphene citrate and metformin and 50 mg/kg b. wt. of the extract while alanine aminotransferase activity in the liver decreased significantly (p<0.05) in Letrozole-induced rats orally administered 100mg/kg per body weight of the extract compared to that of the control animals.

Table 1: Effect of ethanolic extract of Ocimum gratissimum leaves on liver function indices in Letrozole- induced female rats

Groups	Albumin (mg/dL)	Globulin (mg/dL)	Total Protein	Direct Bilirubin	Total Bilirubin	Albumin -Globulin
	(ing/uL)	(ing/uL)	(Ing/uL)	(ing/uL)	(ing/uL)	Tatio (ilig/uL)
Control	6.81 ± 0.69^{a}	$5.60\pm1.01^{\rm a}$	$1.22\pm0.33^{\rm a}$	$5.01\pm0.82^{\rm a}$	$1.56\pm0.55^{\rm a}$	$1.28\pm0.11^{\rm a}$
PCOS+ distil. H ₂ O	$6.84\pm0.08^{\rm a}$	$5.07\pm0.15^{\rm a}$	$1.77\pm0.23^{\rm a}$	$1.29\pm0.68^{\rm c}$	$2.28\pm0.28^{\rm a}$	$1.36\pm0.05^{\rm a}$
PCOS + Met+ CC	$7.12\pm0.12^{\text{b}}$	$6.97\pm0.11^{\rm a}$	0.16 ± 0.20^{b}	$8.56\pm0.52^{\rm b}$	$0.31\pm0.16^{\rm a}$	$1.02\pm0.00^{\text{b}}$
PCOS + 50mg/kg b.w. of EEOGL	$7.50\pm0.44^{\rm a}$	$6.04\pm0.43^{\rm a}$	$1.47\pm0.01^{\rm a}$	$4.35\pm0.58^{\rm a}$	$1.19\pm0.48^{\rm a}$	$1.25\pm0.01^{\rm a}$
PCOS + 100mg/kg b.w. of EEOGL	$8.03\pm0.41^{\rm a}$	$6.75\pm0.89^{\rm a}$	$1.28\pm0.47^{\rm a}$	$0.47\pm0.12^{\rm c}$	6.74 ± 2.37^{b}	$1.23\pm0.10^{\rm a}$
Data are expressed as means of four	determinations + SEM	Values with different su	perscripts in each colun	on are significantly differe	ent (p<0.05). MET- Met	formin, CC- Clomiphene

Data are expressed as means of four determinations \pm SEM. Values with different superscripts in each column are significantly different (p<0.05). ME1- Metformin, CC- Clomiphene citrate

EEOGL

Groups	Creatinine (mg/dl)	Urea (mg/dl)	Uric acid (mg/dl)	Blood urea nitrogen ratio (mg/dl)
Control	$0.34\pm0.38^{\rm a}$	1.05 ± 0.26^{a}	$0.64\pm0.00^{\rm a}$	2.98 ± 0.44^{a}
PCOS+ distil. H ₂ O	$0.53\pm0.00^{\rm b}$	$0.89\pm0.00^{\rm a}$	$2.27\pm0.00^{\text{b}}$	$1.68\pm0.00^{\rm a}$
PCOS + Met +CC	$0.50\pm0.00^{\rm b}$	$3.27\pm0.00^{\rm c}$	$3.34\pm0.00^{\rm c}$	$6.54\pm0.00^{\rm a}$
PCOS + 50mg/kg b.w. of EEOGL	$0.80\pm0.01^{\circ}$	$2.53\pm0.00^{\rm b}$	$9.39\pm0.00^{\rm d}$	33.74 ± 4.87^{b}
PCOS + 100mg/kg b.w. of	0.22 ± 0.00^{d}	6.12 ± 0.34^{d}	$20.61 \pm 0.00^{\circ}$	28.48 ± 1.98^{b}

Table 2: Effects of administration of ethanolic extract of *Ocimum gratissimum* leaves on some kidney function indices of Letrozole-induced female rats

Data are expressed as means of four determinations ± SEM. Values with different superscripts in each column are significantly different (p<0.05). MET- Metformin, CC- Clomiphene citrate

Table 3: Aminotransferase activi	y in the liver and serum of PC	OS rats administered EEOGL
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Groups	Serum AST	Liver AST	Serum ALT	Liver ALT
Control	69.08 ± 0.05^{a}	$106.08 \pm 0.05^{\rm a}$	21.00 ± 0.00^{a}	$75.00\pm0.00a$
PCOS+ distil. H ₂ O	$62.08\pm0.05^{\text{e}}$	$94.08\pm0.05^{\rm d}$	$22.00\pm0.00^{\text{b}}$	$108.00\pm0.00^{\rm d}$
PCOS + Met +CC	$28.\ 08\pm0.05^c$	$16.08\pm0.05^{\rm b}$	$13.00\pm0.00^{\text{e}}$	$77.00\pm0.00^{\rm b}$
PCOS + 50mg/kg b.w. of EEOGL	$56.08\pm0.05^{\text{d}}$	$104.08\pm0.05^{\rm e}$	$6.00\pm0.00^{\rm d}$	$84.65\pm0.06^{\rm c}$
PCOS + 100mg/kg b.w. of EEOGL	96.08 ± 0.05^{b}	$47.08\pm0.05^{\rm c}$	$41.65\pm0.06^{\rm c}$	$8.00\pm0.00^{\text{e}}$

Data are expressed as a means of four determinations ± SEM. Values with different superscripts for each group are significantly different (p<0.05). MET Metformin, CC- Clomiphene citrate, AST- Aspartate aminotransferase, ALT- Alanine aminotransferase

Table 4: Alkaline phosphatase activity in the liver and serum of PCOS rats administered EEOGL

Groups	Serum ALP	Liver ALP
Control	$11.88\pm0.00^{\rm a}$	889.32 ± 0.00^{a}
PCOS+ distil. H ₂ O	$297.05\pm0.00^{\text{e}}$	$361.03{\pm}0.00^{\text{e}}$
PCOS + Met +CC	$216.62 \pm 0.00^{\circ}$	$95.06{\pm}0.00^{\circ}$
PCOS + 50mg/kg b.w. of EEOGL	$151.74{\pm}0.01^{b}$	$164.54{\pm}0.01^{\rm d}$
PCOS + 100mg/kg b.w. of EEOGL	$239.49{\pm}0.01^{d}$	$62.17{\pm}0.01^{b}$

Data are expressed as means of four determinations ± SEM. Values with different superscripts in each column are significantly different (p<0.05). MET- Metformin, CC- Clomiphene citrate

DISCUSSION

Ocimum gratissimum (Linn.) leaves in letrozole-induced polycystic ovarian syndrome in Wistar rats has provided added information on the effects of the extract on the liver and kidney of the animals. The need to assess the total protein, albumin, globulin, and bilirubin (Total and direct) levels in the serum of animals together with the administration of chemical compounds such as the ethanolic extract of *Ocimum gratissimum* cannot be overemphasized as they are useful criteria for evaluating not only the secretory ability and or functional capacity of the liver ^[14].

Albumin, globulin, and total bilirubin which make up the cell's protein content can be used to analyze the liver's functional capacity ^[14]. Furthermore, alterations in the serum concentration of albumin, globulin, and bilirubin may indicates impairment in the liver's synthetic and secretory functions as well as the type of liver damage ^[14]. Increased bilirubin concentration in the blood might be caused by increased product ion of bilirubin or reduced liver uptake (as a result of liver diseases) ^[15].

The reduction in the level of computed albumin-globulin ratio by letrozole in this present study may be attributed to letrozole diminishing the biosynthesis of the albumin-globulin ratio and it may reflect overproduction of globulins, such as seen. The unaltered total protein level by letrozole was also maintained by all the doses of the ethanolic extract which suggests normal functioning of the liver in relation to total bilirubin ^[14].

Effects of ethanolic extract of *Ocimum gratissimum* serum total protein, albumin, globulin, and albumin: globulin ratio was examined in this study. From the result obtained, there was a significant increase in albumin and globulin levels of letrozole-induced animals administered orally 50 and 100mg/kg body weight extract (P<0.05). The elevated albumin level by letrozole was further aggravated by the administration of the ethanolic extract suggesting a possible synergistic action between the drug and the extract in this study.

The kidney is known for its ability to remove metabolic waste, maintain balance at optimum pH and maintain chemical balance in the blood ^[16]. Creatinine urea and uric acid are considered to be metabolic waste thus high level of this in blood indicates kidney dysfunctions, damage, or diseases ^[17]. In this study, there are elevated level of creatinine, urea, uric acid as well as BUN- creatinine ratio concentration in Letrozole-induced rats orally administered 50mg/kg per b. wt. of the ethanolic extract and 100mg/kg per body weight of the ethanolic extract when compared with the control animals indicating that the doses have an increase effect of letrozole on the function of the kidney.

The enzymes, AST and ALT, plays a pivotal role in biological processes. They function in the breakdown of amino acids into a-keto acid, which is necessary for complete metabolism through the Krebs cycle and electron transport chain ^[18]. These enzymes are remarkably considered as specific indicators for liver damage.

AST enzyme is found mostly in the liver, but also in muscles. If liver damage occurs, it releases AST into your bloodstream. Dose at 50 mg/kg showed a reduced level in the concentration reversing the effect of letrozole which causes a spike in the level of AST concentration showing that both deses poses no damage and even reverses any damage caused while dose at 100 mg/kg showed an increased level in AST concentration increasing the effect of letrozole.

ALP enzyme helps to denote the state of the plasma membrane and an increase in the level of this enzyme denotes damage done to the plasma membrane ^[14].

Administration of letrozole shows a diminished level of ALP activities in the liver and after administration of 50mg/kg and 100mg/kg of the extract there was a significant decrease in the level of the ALP activity in the liver and serum showing that the extract inhibits the action of ALP activity similar to that of letrozole at the cellular molecular level ^[19].

ALT enzyme denotes the metabolic conditions of the hepatocytes, and a high level of this enzyme shows damages done to the hepatocytes. ALT levels were increased significantly after administration of letrozole in the serum and liver showing a positive effect while there was an increase in the level of ALT activity in the liver and a decrease in the serum after the administration of 50mg/kg of the ethanolic extract of the extract while there was a decrease in ALT activity in the liver and an increase in animals administered 100mg/kg of the ethanolic extract.

CONCLUSION

In conclusion, the toxicological evaluation of the ethanolic extract of *Ocimum gratissimum* leaves reveals that both doses of 50mg/kg and 100mg/kg per B.Wt. of the extract induced either a significant increase or decrease (p<0.05) in the biochemical assessments (liver function indices, kidney function indices) when compared to the control animals without causing any obvious toxic effect on the animals. Although they mild alterations were noticed in the Letrozole-induced female rats when compared to the control animals.

Conflict of Interest

None declared.

Financial Support

None declared.

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