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Effect of Letrozole and toxicity profile of five medicinal plants used in controlling parameters of polycystic ovarian syndrome in female wistar rat.

Ozioko, Eucharia N[1]., Ajibade, GA[2]., Vantsawa, PA[3]. Appah, J.[4] and Avidime Solomon[5]

[1]Biology Department Airforce Institute of Technology, Kaduna, Nigeria
[2] Biology Department, Nigeria Defence Academy, Kauna, Nigeria
[3] Biology Department, Nigeria Defence Academy
[4] Biology Department, Nigeria Defence Academy
[5] Department of Obstrecial Gyneacology, Ahmadu Bello University, Zsaria

Abstract

Acute toxicity test of the five plant extracts, namely: *Trigonella foenum graecum*, *Glycine max*, *Sesame indicum*, *Glycyrrhiza glabra* and *Lepidium meyenii* was performed using Karbers method prior to the experiment. The experimental animals, female wistar rats, were grouped into twelve, and necessary body statistics taken before each group was treated with letrozole for twenty one days before the plant extract at either 300mg/kg or 100mg/kg per body weight, with a normal control and a PCOS group (administered letrozole for twenty one days without plant extract). At the end of the experiment the blood samples of the experimental animals were collected for biochemical analysis. Base on the harmonized 5 point standards for acute toxicity rating of drugs, *T. feonum graenum*, *S. indicum* and *L. meyenni* ethanolic plant extract fall under category 4, since their acute toxicity was $\geq$2000mg/kg while *G. max* and *G. glabra* fall under category 5, since their acute toxicity was $\geq$5000mg/kg. This invariably implies that the plant extracts are safe (zero mortality<2) for human consumption. This research outcome suggests that letrozole can cause increase in weight (invariably PCOS cause increase in weight), increase in the ALP level of the liver to 505.4µ/L and also increase in the creatinine level of the kidney to 1.13mg/dl. The five plant extract used effectively reversed the effect of letrozole in both the kidney and the liver. The activity of the plant extract was observed to be dose dependant, as the extract with higher dose (300mg/kg) show healthy kidney and liver function test than the 100mg/kg. The plant, *T. feonum graenum* however, appeared to be the safest plant and the overall best in reversing the effect of letrozole on both the kidney and the liver and show no toxic effect on both vital organs.

Keywords: Polycystic ovarian syndrome, letrozole, Acute toxicity, Creatinine, Urea,

Introduction

Letrozole is grouped under the class of drugs called aromatase inhibitors. The Aromnatase are enzymes that performe the function of oestrogen production in the body. They are used to treat a type of breast cancer that is known as hormone receptor positive breast cancer that normaly occurs in women after menopause. This type of breast cancer grows with increase in oestrogen and therefore letrozole function by reducing the oestrogen level thereby preventing the cancer from growing. In humans the drug letrozole is use to induce ovulation in women with polycystic ovarian syndrome (PCOS) and other unexplained infertility issues. Letrozole was initially approved by the USA food and drug administration for the treatment of breast cancer, however in 2001, Gynecologists started using it for fertility treatment in place of clomid because letrozole has a fewer side effect than clomid. This does not mean that letrozole is free of any side effect, as side effect such as bloating, blurred vision, breastpain, difficulty in breathing, headache has been reported by (ReachelGurevich 2020).

In Wistar albino rats, letrozole was reported by Kafali *et al*, (2004), to induce parameters of polycystic ovarian syndrome due toincrease ovarian cyst, increase in testosterone, decrease in FSH, increasein Luteinizing hormone and reduce progesterone in them. Polycystic ovarian syndrome (PCOS) is the pathology effect of the structure and function of the ovaries, (Teeda *et al*., 2010, Mayo Clinic 2020, Wekker et al 2020). It is a complex endocrine condition which involves disorder in the hypothalamic pituitary and ovarian network, resulting in chronic anovulation and androgen excess Tabassum *et al*, (2021) and Aflatounian *et al* (2020). Polycystic Ovarian Syndrome leads to excess secretion of androgen hormones which impaired the activities of the ovary (growth and releases of mature follicle), as a result fluid filled sacks (cyst) are formed around the ovary. Clinical presentation of PCOS include infertility, menstrual disorder, baldness, acne zehora *et al*, (2018), obesity, insulin, resistance, sleep apnea, dyslipidemia, impaired insulin tolerance Smeltzer *et al.*, (2010).

Yavari *et al.*, (2016), reported *Sesamum indium* seed extract given to women with Oligomenorrhea for 8 weeks show menstrual bleeding but not significantly different from the group administered progesterone supplement however,the groups given *sesame indium* had higher menstrual cycles than the progesterone supplement group in the drug free cycle. The extract of *Trigonella foecum graceum in* combination with metformin improves mentral cycle (Abrasian *et al* 2018). Swaroop *et al*., (2015), also reported 1000mg extract of *Trigonella foecum graceum* (furocyst) given to females with PCOS over a period of 90days consecutively reveal 46% reduction in cyst,36% complete dissolution of cyst and 71% return of menstruation, at the completion of treatment 12% became pregnant. The patients used for the experiment were between the ages of 18 years and 45years with BMI (Body Mass Index) of 142. 50 and 100mg/kg isoflavone of soya beans administered to female with PCOS for 14 days show antiandrogenic and oxidative activities, Abrasian *et al.*,(2018). 18mg of soya beans supplement (Genistein) administered twice daily to females with PCOS significantly reduced LH level,triglyceride, low density lipoprotein cholesterone,(2DL) dehydroapiandrostrone sulphate (DHEAS) and testosterone, khani*et al.*,(2011). Zatollah Aseni 2016, also report the isoflavone extract of soya beans reduces, circulating blood sugari.e it can control insulin resistance, lowers testosterone level and harmful cholesterone and triglycerides. *Glycrrhiza glabra;* 7g per day administration of the ethanolic extract of plant, increase the aromatization of testosterone level to 17 beta oesradiol, this reduce the testosterione level of females with PCOS and increase their oestradiol level (Arentz *et al* 2014,Yang *et al* 2018). *Lepidium meyennii* (Maca) was reported by Sudhakar *et al* (2017), as a natural hormonal balancer and also help to increase progesterone and astradiol level in PCOS patients.

Materials and Methods

Letrozole was purchase from Andy pharmacy in central market Kaduna State of Nigeria.

Experimental animals used; One hundred and thirty nine (115) female rats were purchased from institute of Trypanosomiasis Research Kaduna, Kaduna state. The rats were allowed to acclimatize with animal house conditions for two weeks. They were caged in a standard rat cage and were allowed free access to food and water. This investigation was carried out in accordance with the international accepted principles for laboratory animals' use and care (NIH) publication no 83, 1985.Moreso, ethical clearance approval for the research was collected from Nigerian Defence Academy Ethical committee.

Preparation of plant extract; The plants were purchased from herbal market in central market Kaduna, Kaduna State, Nigeria. It was then taken to the department of Biological Sciences. Nigerian Defence Academy for identification. The Extraction process was carried out in chemistry Department Nigeria Defence Academy, Kaduna State Nigeria. The plants were raised with distilled water. Dried and grounded to powder. 800g of each of the grinded powder of all the plant was separately soaked in 1500ml of ethanol and extracted in a soxlet extractor apparatus and the ethanolic extract evaporated with a rotary machine and the residue treated to powder. All the plant extract was dissolved in a saline solution before being administered to the animals, this method is similar wit the method of (Hamza *et al.*, 2019).

Acute toxicity test (LD_{50})

This is an undesired effect (harmful effect) of a substance administered to an animal(s) either immediately or a short time (24) after a single administration or multiple administrations, (Chinedu *et al.*, 2013). This experiment was carried out in the Animal House, Biology department, Nigeria Defence Academy, Kaduna state Nigeria. Karbers method was used in this experiment. The animals were grouped into three groups of 5rats each, and this was repeated for each plant sample to be used in the experiment. The doses used are 5000, 2000 and 1000; the first group was administered normal saline. The two key parameters that were considered are, the mean number of mortality recorded across the groups and the dose difference across the groups. These two parameters are in agreement with Karbers method of acute toxicity text which is the methodology adopted.

Karbers methods have this formular

LD	=	Meadian lethal dose
a	=	Dose difference
LD_{50}	=	$LD_{100} – E(axb/n)$
b	=	mean mortality-
n	=	Group population

Administration of letrozole and plant extract

After the animals were allowed to acclimatize for two weeks, their body weights were taken before they were then randomly placed on various selected groups and then administer letrozole at 1mg/kg per body weight. They were grouped into twelve each containing three rats. A group serves as the normal control that was administered water at random and another group serves as the PCOS group, this group was not administered any plant extract. After twenty one days administration of letrozole to the eleven groups, the various plant extracts were then administered at either 300mg/kg or 100mg/kg respectively to each group.

Biochemical analysis

After the fifteen days administration of the plant extract to experimental animals, they were then administered ketamine to sedate them and 4ml of their blood withdraw 5ml syringe. 1ml of the blood was poured into EDTA bottles while the remaining 3ml was then poured into plain sample botlescontainer. The Biochemical analysis was carried out using an automatic chemical analyser macine. The following biochemical parameters were then analyse; Aspartate aminotransferase, Alanine phosphate, Alkaline phosphate, urea, creatinine, potassium, chloride, sodium, lipid profile, glucose level, hormonay assay and bicarbonate.

Results

After the twenty one days administration of letrozole the experimental animals show significant increase in weight (Table 1). At the end of the acute toxicity studies, there was no mortality recorded (Table 2), but that notwithstanding there was autopsy carried out on the internal organs that reviews some possible pathological damages on the vital body organs (Table 3). The results of the liver function test(Table 4), show increase in the ALP level of the letrozole group but however, the AST and ALT level fall within the normal range across all treatment group.

Table1 Weight of animals before and after administration of letrozole

Treatment Groups	Before	After	Difference	P values
Trigonella feonum graecum 300mg/kg	233.3 ± 28.9	264 ± 5.19	+30.7	0.237
Trigonella feonum graecum 100mg/kg	216.7 ± 28.9	229.7±23.9	+13	0.064
Glycine max 300mg/kg	226.7 ± 20.8	241.7±18.8	+15.1	0.013
Glycine max 100mg/kg	226.7 ± 5.77	242.3±7.37	+15.7	0.006
Sesame indicum 300mg/kg	203.3 ± 45.1	214.3±48.5	+11.1	0.049
Sesame indicum 100mg/kg	230.0 ± 26.5	242.3±27.1	+12.3	0.005
Glycyrrhiza glabra 300mg/kg	261.0 ± 18.2	254.3±21.9	+6.7	0.694
Glycyrrhiza glabra 100mg/kg	200.0 ± 0.00	206.0±6.08	+6	0.230
Lepidium meyenii 300mg/kg	226.7 ± 40.4	223.3±37.1	+6.6	0.713
Lepidium meyenii 100mg/kg	237.3 ± 44.0	243.7±50.1	+6.4	0.210
Normal control	241.7 ± 38.2	211.0±38.9	_30.7	0.464
PCOS Group	216.7 ± 28.9	229.7±23.9	13.0	0.064

Values are given as mean ± standard deviation (SD). In each column, values with different superscripts have statistical significant difference ($p< 0.05$).

Table 2 Results of acute toxicity studies

Plant Samples	5000mg/kg (LD50)	2000mg/kg(LD50)	1000mg/kg(LD50)	Total Mortality
Trigonella feonum graeum	No mortality	No motality	No mortality	Zero mortality
Glycine max	No mortality	No mortality	No mortality	Zero mortality (<2)
Sesame indicum	No mortality	No mortality	No mortality	Zero mortality (<2)
Glycyrrhiza glabra	No mortality	No mortality	No mortality	Zero mortality (<2)
Lepidium meyenii	No mortality	No mortality	No mortality	Zero mortality (<2)
Normal control	No mortality	No mortality	No mortality	Zero mortality (<2)

Clinical signs observed after administration of plant extract.

After the administration of the plant extract for toxicity studies the experimental animals appeared normal, feeding normal, no stooling, no sign of illness was observed.

Table 3 Autopsy studies carried out after acute toxicity studies.

Plant samples	Liver	Kidney	Heart	Spleen	Stomach
Trigonella 5000mg/kg	Inflammation of the liver and liver cirrhosis	Normal	Normal	Normal	Normal
Trigonella s 2000mg/kg	Normal	Normal	Normal	Normal	Normal
Trigonella 1000mg/kg	Normal	Normal	Normal	Normal	Normal
Glycine spp 5000mg/kg	Normal	Normal	Normal	Normal	Normal
Glycine spp 2000mg/kg	Normal	Normal	Normal	Normal	Normal
Glycine spp 1000mg/kg	Normal	Normal	Normal	Normal	Normal
Sesame spp 5000mg/kg	Fatty degeneration of the liver and liver cirrhosis	Normal	Normal	Normal	Normal
Sesame spp 2000mg/kg	Normal	Normal	Normal	Normal	Normal
Sesame spp 1000mg/kg	Normal	Normal	Normal	Normal	Normal
Glycyrrhiza 5000mg/kg	Normal	Normal	Normal	Normal	Normal
Glycyrrhiza 2000mg/kg	Normal	Normal	Normal	Normal	Normal
Glycyrrhiza 1000mg/kg	Normal	Normal	Normal	Normal	Normal
Lepidium 5000mg/kg	Normal	Normal	Normal	Normal	Normal
Lepidium 2000mg/kg	Liver cirrhosis	Normal	Normal	Normal	Normal
Lepidium 1000mg/kg	Normal	Normal	Normal	Normal	Normal

Table 4. Biochemical analysis of the liver enzymes of all the groups after fifteen days treatment with plant extracts.

Treatment groups	AST (11.95 – 117.74IU/L)	ALT (16 – 48IU/L)	ALP (60 - 205IU/L)
Trigonella 300mg/kg	13.1 ± 0.50^{b}	26.7 ± 1.06^{abc}	203.8 ± 6.85^{cd}
Trigonella 100mg/kg	12.3 ± 0.45^{ab}	27.3 ± 0.81^{abc}	189.2 ± 4.02^{b}
Glycine max 300mg/kg	13.5 ± 0.66^{b}	28.1 ± 0.26^{abc}	212.1 ± 1.81^{d}
Glycine max 100mg/kg	16.1 ± 0.26^{c}	23.9 ± 0.70^{ab}	242.4 ± 3.10^{f}
Sesamum 300mg/kg	15.9 ± 0.47^{c}	44.2 ± 0.35^{d}	167.9 ± 1.29^{a}
Sesamum 100mg/kg	12.7 ± 0.56^{b}	31.6 ± 3.20^{c}	185.8 ± 5.09^{b}
Glycyrrhiza 300mg/kg	12.8 ± 0.46^{b}	23.9 ± 0.55^{ab}	212.4 ± 0.96^{d}
Glycyrrhiza 100mg/kg	10.8 ± 0.60^{a}	22.1 ± 0.98^{a}	222.5 ± 0.75^{e}
Lepidium 300mg/kg	18.7 ± 0.70^{d}	29.3 ± 0.91^{bc}	210.1 ± 0.76^{d}
Lepidium 100mg/kg	14.1 ± 0.70^{a}	24.4 ± 1.11^{ab}	199.8 ± 0.56^{c}
PCOS	68.5 ± 2.74^{e}	61.4 ± 2.04^{e}	$505.4+11.9^{g}$
Normal Control	12.8 ± 0.36^{b}	213.3 ± 10.8^{f}	204.5 ± 3.81^{cd}
p value	< 0.0001	< 0.0001	< 0.0001

Values are given as mean ± standard deviation (SD). In each column, values with different superscripts have statistical significant difference ($p< 0.05$).

AST; Aspartate aminotransferase, ALT; Alanine phosphate, ALP; Alkaline phosphate.

Table 5. Biochemical analysis of the kidney enzymes

Treatment Groups	Urea(2.45-3.11)	Creatinine (0.5-1.0)
Trigonella spp 300mg/kg	2.90±0.17^{d}	0.47±0.06^{a}
Trigonella spp 100mg/kg	2.63±0.06^{c}	0.87±0.06^{de}
Glycine max 300mg/kg	1.97±0.05^{a}	0.53±0.12^{ab}
Glycine max 100mg/kg	3.30±0.26^{f}	0.47±0.12^{a}
Sesame indicum 300mg/kg	2.30±0.10^{ab}	0.63±0.12^{abc}
Sesame indicum 100mg/kg	2.67±0.06^{b}	0.97±0.06^{e}
Glycyrrhiza spp 300mg/kg	2.07±0.12^{c}	0.87±0.06^{de}
Glycyrrhiza spp 100mg/kg	3.07±0.11^{ab}	0.77±0.06^{f}
Lepidium meyenii 300mg/kg	3.27±0.11^{de}	0.77±0.06^{cd}
Lepidium meyenii 100mg/kg	3.26±0.12^{e}	0.53±0.11^{ab}
PCOS	2.17±0.06^{ab}	1.13±0.12^{f}
Normal control	2.67±0.12^{c}	0.67±0.06^{bc}
P Value	<0.0001	<0.0001

Values are given as mean ± standard deviation (SD). In each column, values with different superscripts are statistically significantly different (p< 0.05).

Table 6. Biochemical analysis of the kidney electrolytes of all the treatment groups after fifteen days treatment with the plant extracts

Treatment Groups	Sodium (100-120)	Potassium (3.3-5.1)	Chloride (100-107)	Bicarbonate (16-24)
Trigonella spp 300mg/kg	98.7±0.58^{d}	4.13±0.12^{a}	100.6±1.15^{c}	21.6±1.15^{d}
Trigonella spp 100mg/kg	113.3±0.58^{e}	7.30±0.44^{e}	90.6±1.15^{ab}	18.7±1.15^{a}
Glycine max 300mg/kg	97.7±2.52^{d}	5.27±0.64^{bc}	102.6±1.15^{c}	16.6±1.15^{a}
Glycine max 100mg/kg	123.3±0.58^{g}	6.40±0.17^{d}	89.7±1.15^{c}	22.7±1.15^{d}
Sesame spp 300mg/kg	76.0±1.73^{a}	6.10±0.17^{d}	100.7±1.15^{c}	19.7±1.15^{bc}
Sesame spp 100mg/kg	87.3±1.15^{c}	4.13±0.12^{a}	88.0±1.73^{a}	22.0±1.73^{cd}
Glycyrrhiza 300mg/kg	106.7±2.52^{e}	4.20±0.17^{a}	100.7±1.15^{c}	21.6±1.15^{d}
Glycyrrhiza 100mg/kg	122.0±1.73^{g}	5.46±0.12^{c}	102.0±1.73^{c}	18.7±1.15^{ab}
Lepidium spp 300mg/kg	75.0±1.00^{a}	5.47±0.11^{bc}	88.0±1.73^{a}	16.6±1.15^{a}
Lepidium 100mg/kg	81.7±1.53^{b}	6.36±0.^{12}d	102.7±1.^{15}c	22.0±1.^{d}
PCOS	91.3±5.77^{c}	4.90±0.66^{b}	93.3±4.16^{b}	20.7±0.57^{bcd}
Normal control	101.7±4.04^{d}	4.83±0.29^{bc}	100.0±3.46^{c}	22.0±12.73^{cd}
P Values	<0.001	<0.001	<0.001	<0.001

Values are given as mean ± standard deviation (SD). In each column, values with different superscripts are statistically significantly different (p< 0.05).

Discussion

After twenty one days of administration of letrozole to the experimental animals, the animals were found to gained weight significantly when compared to the normal control group, this increase in weight of the animals is in agreement with the report of Ehrmann *et al*, (2006), who reported that females with PCOS develop obesity as a result of excess androgen secretion. Sam (2007), also reported that PCOS is responsible for 80% Obesity common among US women. Insulin resistance could be another reason for this increase in weight, this is because insulin is a hormone produced by the pancreas and it perform the primary function of regulating the sugar level in humans and Female with PCOS who are resistant to this hormone and this result to high level of sugar in the body which then lead to obesity and high level of insulin in blood as they tend to produce more insulin to control the high sugar level in the body. This high level of insulin causes high level of androgen which causes anovulation in females with PCOS (Mayo Foundation, 2019). At the end of the toxicity test, since there was no mortality, the experimental animals were sacrificed and their internal organs were examined. The autopsy results indicates the following; *T. graecum*; the 1000mg/kg and 2000mg/kg per body dosage had no effect on the liver, kidney, heart, spleen, pancreas, gall bladder, thymus, diaphragm, stomach and intestines, but the 5000mg/kg cause inflammation of the liver and there was presence of white patches in the liver indicating liver cirrhosis. *G. max;* the 5000mg/kg, 2000mg/kg and 1000mg/kg per doses had no advanced effect on all the internal organs, as all the organs appeared normal. *S. indicum;* the 1000mg/kg and 2000mg/kg body dosage had no effect on the internal organs however the 5000mg/kg show inflammation of the liver, white patches on the liver, indicating possible fatty degeneration, liver cirrhosis and inflammation. *G. glabra*; 5000mg/kg, 2000mg/kg and 1000mg/kg doses had no effect on all the internal organs. *L. meyenii;* the 1000mg/kg and 2000mg/kg dosage had no toxic effect on all the internal organs, as all organs appeared normal but at 5000mg/kg there was white patches on the liver indicating possible liver cirrhosis.AST; Aspartate aminotransferase, ALT; Alanine phosphate, ALP; Alkaline phosphate, are important biomarkers of the liver, heart, pancreas, kidney and Bilary duct injury. The increase in the blood level of these biomarkers tell that the above listed organs are either damage or in a diseased condition. Most important of them are the AST and ALT, when liver function test is the main interest because when there is any damage in the liver organs it is these two biomarkers that are released in high quantity in the blood, an increase in ALP on the other hand could either be as a result of blockage of the bile duct, liver damage, increase in protein consumption or from the bones, as ALP perform the function of breaking down protein. When there is excess consumption of protein the body releases more ALP. The result of the liver function test, indicate that all the plant extract had no negative impact or cause no toxic effect on the internal organ (liver) as the AST and ALT levels were within their normal range, however the ALP level of the letrozole group was significantly higher than all treatment group (505.4µ/L), this report further buttresses the findings of Yonden *et al.*, 2009, they reported that letrozole increases the ALP level of female rats they used in their experiment they concluded by saying that letrozole increases the risk of bone fracture. Although the ALP values from other treatment groups show that the negative effect of letrozole on the liver enzymes was decreased however, significant reversal was seen in *T. graenum*, at both 300mg/kg and 100mg/kg , *S. indicum* at both 300mg/kg and 100mg/kg and *L. meyenii* at 100mg/kg, because their values fall within the normal range. In the kidney function test, the PCOS group shows increase in creatinine (1.13mg/dl), and a decrease in sodium (91.3mg/dl) and chloride level (93.3mg/dl), this finding is in agreement with the submission of Fadia *et al*, (2020), they reported increase in creatinine and acute interstitial nephritis in patients treated with letrozole. The values obtained from the kidney function test proved that all the plant extract used completely reverse the effect of increase in creatinine level as reported in the PCOS group except for the group treated with *G. glabra* at 100mg/kg that has high creatinine level like PCOS group. The group treated with *T.graenum* at 300mg/ml and 100mg/kg show

complete reversal of the effect of letrozole on the kidney enzymes and also show no toxicity effect on kidney tubules as all the electrolytes fall within their normal range. The values obtained from the group treated with *Glycine max* at both 300mg/kg and 100mg/kg show toxicity effect on the kidney tubules (ability to reabsorb electrolytes) as there was increase in urea level, slight increase in creatinine, increase in sodium, increase in potassium and decrease in chloride level. In the group treated with *S. indicum* the urea, creatinine and the bicarbonate fall within the normal range but the other electrolytes show malfunctioning of the kidney tubules. The results of the kidney function test of the group treated with *L. meyenii* at both 300mg/kg and 100mg/kg show signs of glomerulonephritris because the urea and other electrolytes were either too low or the too high apart from the bicarbonate. The urea is filter in the glomerulus while the electrolytes are been reabsorbing in the kidney tubules.

Conclusion

According to the standard acute toxicity rating of drugs, *T. graenum, S. indicum* and *L. meyenni* ethanolic plant extract fall under category iv, since their acute toxicity is ≥2000mg/kg while *G. max* and *G. glabra* fall under category v, since their acute toxicity is≥5000mg/kg This invariably means that the plant extract is safe for human consumption. This research outcome suggest that letrozole cause increase in weight (invariably PCOS cause incease in weight), increase in the ALP level of the liver and also increase in the creatinine level of the kidney. The five plant extract used effectively reversed the effect of letrozole in both the kidney and the liver through a significant moderation of the negative effect of letrozole on these vital body organs. The activity of the plant extract is dose dependant, as the extract with higher dose (300mg/kg) show better healthy kidney and liver function test than 100mg/kg however; *T. graenum* was considered the safest of the tested plant extracts and the overall best in reversing the effect of letrozole on both the kidney and the liver.

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