Official Journal Issued by Faculty of Veterinary Medicine

Benha Veterinary Medical Journal

Journal homepage: https://bvmj.journals.ekb.eg/

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Original Paper

The protective potential of ginseng on ciprofloxacin-induced male gonadotoxicity.

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ARTICLE INFO

Keywords

Fluoroquinolones

Panax ginseng

Reproduction

Spermatogenesis

Received 25/05/2022
Accepted 26/06/2022
Available On-Line 01/10/2022

ABSTRACT

Drug-induced infertility is an important etiology and a common side effect. It is, therefore, important to develop newer pharmacological approaches to vanquish this bad effect. The aim of the present study is to evaluate the possible protective potential of ginseng against ciprofloxacin-induced male gonadotoxicity. Sixty adult Wister albino male rats (8 weeks old, 200 ± 20gm) were randomly divided into six groups of tens. Groups 1 and 2 received 78.23 and 156.46mg/kg/day of ciprofloxacin, respectively. Groups 3, 4 and 5 received 156.46 mg/kg/day of ciprofloxacin plus 100 mg/kg/day ginseng, 200mg/kg/day ginseng, and 100 mg/kg/day vitamin E, respectively. However, the sixth group served as control and received NS and CMC. All treatment given orally for 14 days. Half of the animals of each group has been sacrificed on the day 15, while the second half was sacrificed on the day 60 from the start of the treatment, after blood sampling. Immediately after dissection, testis, epididymis, prostate, and seminal vesicle were removed and weighted. Reproductive organ weights were decreased, sperm parameters were impaired and FSH and LH levels were increased in groups 1 and 2 but still normal in groups 3, 4 and 5 on the two sacrifice days. Testosterone level was significantly decreased in groups 1 and 2. However, higher levels were shown with low and high doses of ginseng treatment. Adding ginseng or vitamin E could protect against ciprofloxacin-induced infertility in the two sacrifice days.

1. INTRODUCTION

Ciprofloxacin is a second-generation, strongly synthetic fluoroquinolone antibiotic, and it has bactericidal activity against a wide variety of bacterial infections (Thai et al., 2021). Genitourinary tract infections adversely affect the reproductive system of the male. Some of these effects are caused by oxidative stress events; Ciprofloxacin is a choice antibacterial agent in the treatment of these infections (Calogero et al., 2017). Ciprofloxacin can also induce apoptosis through oxidative damage in testicular tissue (Shokri et al., 2015). Ciprofloxacin significantly impairs both testicular function and structure in rats (Abd-Allah et al., 2000), reduces sperm count, motility, and daily sperm production in rats, and adversely affects male fertility (Xie et al., 2019). Oxidative stress is one of the most accused of causing infertility (Mokhimar et al., 2020), hypothesizing that Ginseng is a proven potent antioxidant and might protect from the adverse effects of Ciprofloxacin.

Ginseng is always referred to be the King of all herbs and is used to treat sexual dysfunction also enhancing sexual behavior (Leung and Wong, 2013). Ginseng is a potent antioxidant that has a wide range of actions such as; anti-aging, immune-enhancing, anti-stress, and anti-cancerous (Cheng et al. (2006); (Kang et al., 2006). Ginseng has been shown to stimulate spermatogenesis and improve testicular functions and sperm quality (Sengupta and Dutta, 2022). Concomitant use Ginseng and Ciprofloxacin improve sperm quality and spermatogenic cells (Sanad et al., 2021a). Therefore, the present study primary aim is to illustrate Ginseng's potential protective effect against Ciprofloxacin-induced gonadotoxicity and hormonal changes. To achieve this aim, the following objectives have been carried out: 1-effect of Ciprofloxacin and Ciprofloxacin with Ginseng on reproductive organs weight, 2-effect of Ciprofloxacin and Ciprofloxacin with Ginseng on sperm parameters, 3-effect of Ciprofloxacin and Ciprofloxacin with Ginseng on reproductive hormones, 4-effect of Ciprofloxacin and Ciprofloxacin with Ginseng on the histological structure of testis.

2. MATERIAL AND METHODS

2.1. Drug preparation:

Ciprofloxacin was purchased as a generic pharmaceutical preparation Serviflox® with a concentration of 750 mg of Ciprofloxacin in one tablet manufactured by Novartis pharma-Cairo, under the license of Sandoz GmbH-Australia. The tablets were crushed and diluted with CMC in NS to a final volume of 1ml /rat dose. Ginseng was purchased with the generic name Ginsana® with a concentration of 100mg of Ginseng in one capsule manufactured by Egyptian International Pharmaceutical Industries Company (EIPICO). The capsules were opened and diluted with CMC in NS to a final volume of 1ml /rat

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dose. Vitamin E was purchased as a generic name vitamin E 1000® with a concentration of 1000 mg of vitamin E in each capsule manufactured by Pharco pharmaceuticals. The capsules were opened and diluted with sunflower oil to a final volume of 1ml /rat dose.

2.2. Animals:

Sixty adult Wister albino male rats, 8 weeks old and weighing 200±20g, were used. They were obtained from Animal House, Faculty of Veterinary Medicine, Benha University. Male rats were housed at average room temperature (30°C) with humidity (40-60%) and 12h/12h dark/ light cycle before the start of the experiment. The animals were fed laboratory formula and tap water ad libitum.

2.3. Study design:

After two weeks of adaptation to a standard diet, 60 rats were randomly divided into one of the six groups, with ten rats in each group. Rats in groups 1 and 2 received PO ciprofloxacin in two divided daily doses of 78.23 and 156.46mg/kg, respectively. Rats in group 3&4&5 received PO ciprofloxacin at a daily dose of 156.46mg/kg and OD ginseng in two doses of 100 and 200mg/kg and vitamin E in a daily dose of 100mg/kg, respectively. Group 6 served as control and received PO 1 ml CMC in NS. All treatments were orally administered for 14 days. Half the animals in each group were sacrificed by decapitation on day 15 from the start of the treatment (1st sacrifice), while the second half was sacrificed on day 60 from the start of the treatment (2nd sacrifice). After blood sampling and dissection of the rat, testis, epididymis, prostate, and seminal vesicle were Immediately removed and weighed.

2.4. Blood sampling:

Blood samples were collected from the retro-orbital venous plexus located at the eye's medial canthus by heparinized capillary tubes. Plasma samples were separated and kept frozen in the refrigerator (-20 °C) for analysis of total testosterone, FSH, and LH using rat ELISA kits under the commercial name of Fine-Test kits (Wuhan Fine Biotech Co., Ltd.).

Histopathology of the testis:

The testis was fixed in formalin 10% then five-micron thick tissue paraffin sections were routinely prepared and stained with hematoxylin and eosin using a standard technique described by (Bancroft and Gamble, 2002).

2.5. Sperm parameter assessment:

Sperms were collected from the tail of the two epididymis by cutting them into small pieces in a petri dish containing 2 ml of saline (0.9% NaCl). For counting and estimating sperm progressive motility, a small drop of a semen sample was taken and placed on a warm, clean glass slide using a microscope at 400x magnification. Two types of seminal smudge slides were obtained from each animal; one was stained with Eosin and Nigrosine, and the other was fixed in Carnoy's solution for evaluating sperm abnormalities and viability. For sperm counting, let sperms distribute in the solution of 2 ml normal saline then diluted to 10 ml normal saline and kept for 24 hours. A few drops of eosin 2% solution were added to the solution to stain sperm heads to be easily counted (Hackett and Macpherson, 1965).

2.6. Statistical analysis:

A one-way analysis of variance (ANOVA) test was used to perform the multi-group comparisons, followed by post hoc Tukey's test for pairwise comparison at 0.05 level of significance. All groups were compared against the control group (group 6), vitamin E-co-treated group (group 5), and double-dose ciprofloxacin-treated group (group 2).

3. RESULTS

Sexual organs weight:

On the first or the second sacrifice day, the group treated with high-dose Ciprofloxacin showed a significant reduction in the testis weights and the epididymis weights compared to the other groups ($p<0.05$). But there was no significant difference among the ventral prostate weights in all experimental groups (Table 1). On the first sacrifice day, there was a significant reduction in the seminal vesicle weight in the group treated with high-dose Ciprofloxacin compared to the control group ($p<0.05$). On the other hand, treating with a low or high dose of ginseng or vitamin E and a high dose of Ciprofloxacin showed significant restoration of the seminal vesicle weights (Table 1). On the second sacrifice day, all weights were restored to normal. (Table 1)

Table1 Reproductive organ weights comparison among the Wister rat groups treated with ciprofloxacin with and without alpha ginseng or vitamin E, and control.

Day	Group	Testis (g)	Epididymis (mg)	Seminal Vesicle (mg)	Ventral Prostate (mg)
1st	1	1.1 ± 0.04^{CDE}	429 ± 13^{CE}	427 ± 11.7^{CE}	508 ± 26.3
	2	0.87 ± 0.01^{CE}	383 ± 8^{CE}	389 ± 18^{CE}	464 ± 12
	3	1.42 ± 0.04^{DE}	538 ± 12^{D}	540 ± 21^{D}	470 ± 15
	4	1.45 ± 0.02^{D}	545 ± 12^{D}	597 ± 15^{D}	468 ± 23
	5	1.57 ± 0.01^{D}	556 ± 16^{D}	599 ± 5^{D}	498 ± 37
	6	1.52 ± .03^{D}	556 ± 16^{D}	572 ± 14^{D}	486 ± 18
2nd	1	1.75 ± 0.04^{D}	858 ± 23^{CE}	710 ± 41	630 ± 19
	2	1.5 ± 0.03^{CE}	766 ± 27^{CE}	650 ± 33	600 ± 27
	3	1.67 ± 0.04	1067 ± 23^{D}	692 ± 31	636 ± 28
	4	1.67 ± 0.04	1090 ±24^{D}	690 ± 33	638 ± 24
	5	1.74 ± 0.05^{D}	1150 ± 34^{D}	630 ± 23	630 ± 22
	6	1.74 ± .03^{D}	1112 ± 32^{D}	738 ± 27	602 ± 19

Groups 1 and 2 received therapeutic and double dose ciprofloxacin. Groups 3, 4 and 5 received double dose ciprofloxacin plus therapeutic dose ginseng, double dose ginseng, or vitamin-E. Group 6 served as a control. Comparisons among groups were conducted using one-way ANOVA, followed by post hoc Tukey's test. ^{C}: Significant difference in comparison with control. ^{D}: Significant difference in comparison with double dose ciprofloxacin. ^{E}: Significant difference in comparison with double dose ciprofloxacin plus vitamin-E.

Sperm count and progressive motility:
On the first or the second sacrifice day, the group treated with high-dose Ciprofloxacin showed a significant reduction in sperm count and progressive motility compared to the other groups (p<0.05). On the other hand, treating with a low or high dose of ginseng or vitamin E and a high dose of Ciprofloxacin showed significant preservation of the sperm count and progressive motility (Table 2).
Viability:
Either on the first or the second sacrifice day, the group treated with high-dose Ciprofloxacin showed a significant reduction in sperm viability compared to all other groups (p<0.05) (Table 2).
Head abnormality:
A numerically higher but insignificant head abnormality percentage was seen on the first sacrifice day among groups treated with high-dose Ciprofloxacin alone. However, on the second sacrifice day, the increased head abnormalities were significant among the high-dose ciprofloxacin-treated group compared to the low-dose ciprofloxacin-treated, high-dose ginseng-treated, vitamin-E-treated, and placebo-treated groups (p<0.05) (Table2) (Figure1).
Tail abnormality:
Either on the 1st or 2nd sacrifice day, the group treated with high or low-dose Ciprofloxacin showed a significant increase in sperm tail abnormalities compared to all other groups (p<0.05) (Table 2).

Table2 Sperm analysis comparison among the Wister rat groups treated with ciprofloxacin with and without ginseng acid or vitamin E, and control.

Days	Group	Sperm count (10^6/ml)	Progressive Motility (%)	Viability (%)	Head Abnormality (%)	Tail Abnormality (%)
1st	1	18.35 ± 1.05^{CE}	34 ± 3.2^{CE}	70 ± 1.6^{D}	6.4 ± 1.7	71.6 ± 3.6^{CE}
	2	16.95 ± 0.6^{CE}	23 ± 2.2^{CE}	55 ± 3.9^{CE}	9 ± 2.1	76 ± 2.5^{CE}
	3	23.1 ± 0.7^{CDE}	56 ± 6^{CDE}	70 ± 1.6^{D}	9 ± 4.18	38.4 ± 1.7^{CDE}
	4	30.1 ± 3.5^{D}	78 ± 1.3^{D}	72 ± 1.3^{D}	5.2 ± 0.4	22 ± 1^{D}
	5	30.6 ± 3.6^{D}	73 ± 2.2^{D}	72 ± 1^{D}	4 ± 0.6	21 ± 1.7^{D}
	6	29.5 ± 0.75^{D}	73 ± 4.23^{D}	75 ± 1.7^{D}	3 ± 0.63	20.6 ± 2.48^{D}
2nd	1	21.5 ± 1.4^{CE}	48 ± 4.15^{CDE}	54 ± 1.1^{CDE}	3.4 ± 0.9^{D}	50.6 ± 3.5^{CE}
	2	18.35 ± 1.5^{CE}	35 ± 2.4^{CE}	38 ± 1.5^{CE}	8.2 ± 1^{E}	55.2 ± 2^{CE}
	3	31.9 ± 1^{D}	63 ± 4.1^{CDE}	70 ± 2.2^{D}	6 ± 0.4	37 ± 1.1^{CDE}
	4	37.1 ± 0.9^{D}	78 ± 2.3^{D}	72 ± 2.3^{D}	4.6 ± 0.2^{D}	23.4 ± 1.5^{D}
	5	36.7 ± 1.7^{D}	76 ± 2.4^{D}	73 ± 1.3^{D}	5.4 ± 0.4^{D}	19.6 ± 2.1^{D}
	6	36.8 ± 1.09^{D}	76 ± 2.73^{D}	$71 \pm .04^{D}$	5.8 ± .01	$19.2 \pm .02^{D}$

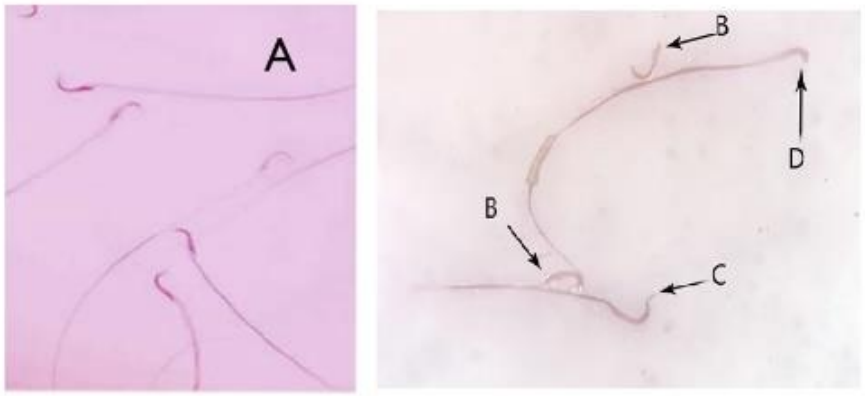

Figure 1 Epidydimal sperms fixed in Carnoy's solution, showing (N) normal sperm morphology, (A): flattened head, (B): detached head, (C): pin head (x1000).

Hormones levels:
Animals treated with high dose ciprofloxacin showed a significant reduction in testosterone level (p<0.05) and a significant increase in FSH and LH levels compared to all groups on 1st sacrifice day. On the other hand, on 2nd day, all animals had normalized testosterone, FSH, and LH serum levels compared to the control. However, the animals treated with low or high Ginseng showed higher testosterone levels (p<0.05) (Table 3).

Table 3 Sexual hormone levels comparison among the Wister rat groups treated with ciprofloxacin with and without ginseng acid or vitamin-E, and control.

Days	Groups	Testosterone Ng/ml	FSH MIU/ml	LH MIU/ml
1st	1	0.89 ± 0.07	2.14 ± 0.1^{CD}	1.5 ± 0.01^{CDE}
	2	0.69 ± 0.06^{C}	4.4 ± 0.1^{CE}	2.6 ± 0.01^{CE}
	3	0.72 ± 0.05^{C}	1.8 ± 0.03^{CDE}	0.99 ± 0.04^{CDE}
	4	0.95 ± 0.02^{DE}	2.4 ± 0.1^{CD}	1.18 ± 0.02^{CDE}
	5	0.69 ± 0.03^{C}	2.2 ± 0.1^{CD}	1.69 ± 0.02^{CD}
	6	0.954 ± 0.06^{DE}	1.2 ± 0.01^{DE}	0.7 ± 0.1^{DE}
2nd	1	0.87 ± 0.02	5.04 ± 0.9	3.0 ± 0.6
	2	0.88 ± 0.05	4.8 ± 0.8	2.8 ± 0.5
	3	1.16 ± 0.7^{CD}	3.56 ± 0.4	2.24 ± 0.2
	4	1.14 ± 0.04^{C}	5.2 ± 0.4	3.1 ± 0.6
	5	0.95 ± 0.12	4 ± 0.5	2.94 ± 0.05
	6	0.84 ± .02	3.44 ± 0.01	1.5 ± 0.2

Histopathological findings:

Histopathological examination of the testes of the negative control group showed the normal histological structure of seminiferous tubules and interstitial tissues (figure2). A marked increase in the destruction of the basement membrane of some seminiferous tubules with distension of its lumen with desquamated germinal cells in groups treated with double dose ciprofloxacin (figure3). On the other side, the testes treated with a high dose of Ciprofloxacin plus a small or high dose of Ginseng showed improvement in histopathological structure. Most seminiferous tubules restored their regular spermatogenic activity (Figure 4). Also, most of the seminiferous tubules were compact with each other and restored their normal histological structure, and the spermatogenic activity is normal in most examined cases when co-administration of vitamin E with Ciprofloxacin (figure5)

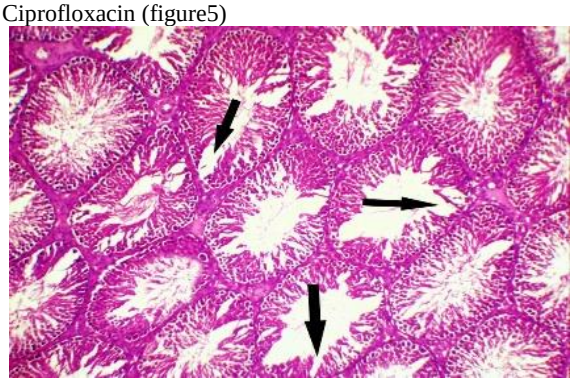

Figure 2 Testis of control rat, group 6, showing normal histological structure of seminiferous tubules (ST) with active spermatogenesis and presence of spermatozoa (arrow) in the lumen (x 100).

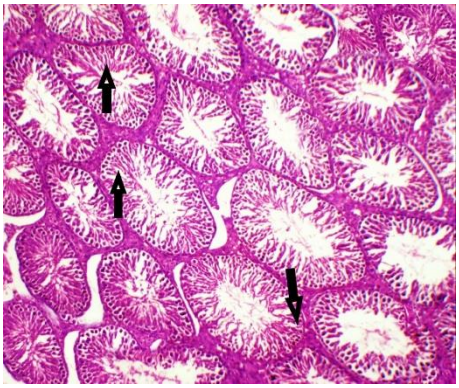

Figure 3 Testes obtained from rat treated with double therapeutic dose of ciprofloxacin showing destruction of the basement membrane of some seminiferous tubules with complete absence of germinal cells (arrows) and distension of its lumen with desquamated epithelial cells (x100).

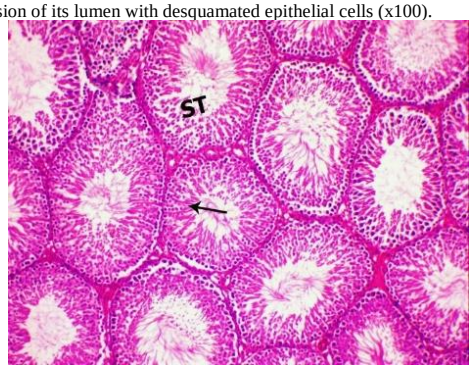

Figure 4 Testes obtained from rat treated with ciprofloxacin plus high dose of ginseng showing normal spermatogenesis in most seminiferous tubules (arrows) (X100).

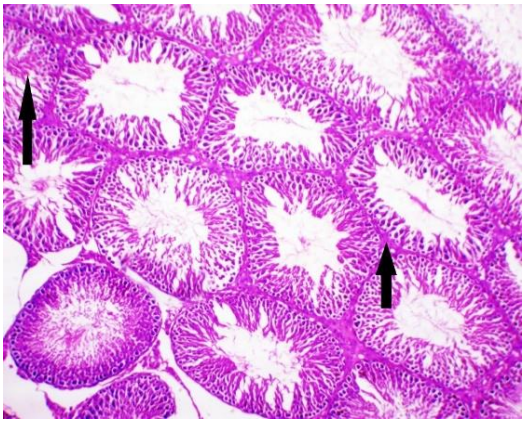

Figure 5 H&E-stained section of testes obtained from rat treated with ciprofloxacin plus high dose of vitamin-E showing most of the seminiferous tubules were compact with each other with normal histological structure of seminiferous tubules and interstitial tissues (arrows) (x100).

4. DISCUSSION

It is well-established that infertility is one of the drug's most crucial side effects (Nudell et al., 2002). So, studying infertility as one of the most acute side effects of drugs is needed. Hypothesizing that Ginseng is a proven potent antioxidant, and it might protect from the adverse effects of Ciprofloxacin, we used Ginseng to treat sexual dysfunction as well as to enhance sexual behavior (Leung and Wong, 2013). Therefore, this study has been performed to evaluate the possible protective effect of Ginseng against infertility induced by Ciprofloxacin using Ginseng in concomitant with ciprofloxacin standard dose 78.23 mg/kg and double standard dose 156.46 mg/kg for 14 days by dosing 100 and 200 mg/kg ginseng in parallel study design. Additionally, we co-administered vitamin E beside the high-dose Ciprofloxacin to another group as a reference antioxidant. The standard dose is calculated as the average dosing of body weight-based and body surface area-based dosing (Mokhimar et al., 2020). Two sacrifice days have been placed, the first was on day 15 to evaluate the acute effects, and the second was on day 60 from the first day of treatment, to follow the sperm cycle from the start of spermatogenesis to sperm maturation (Mahmoudi et al., 2018).

We observed a significant decrease in sexual organ weight (testis, epididymis) and sperm parameters (count, motility, viability) after treatment with Ciprofloxacin. We agree with our findings that Ciprofloxacin had adverse effects on sperm parameters and the male reproductive system (Nashwa et al., 2011). Also, severe histopathological changes and impairment in spermatogenesis were observed in the present study in groups treated with Ciprofloxacin for 14 days compared to other treated groups. Consistently, it has been shown that Ciprofloxacin significantly decreases sperm parameters and concentration decreases in the number of spermatogenic cells and increases apoptosis of germinal cells (Khaki et al., 2008). Also, rats treated with Ciprofloxacin significantly reduced sperm parameters and severe degeneration of germinal epithelium and histopathological changes (Demir et al., 2007). These results are possible due to an increased peroxide radical generation in the testis following ciprofloxacin treatment (Weyers et al., 2002).

On the other hand, the groups which received a small or high dose of Ginseng or vitamin E along with Ciprofloxacin for 14 days showed significant improvement in sexual organ weight and sperm parameters. Similarly to ours, khaki reported that the co-administration of Ginseng and Ciprofloxacin improve sperm parameters and spermatogenesis (Khaki, 2015). Also, Panax ginseng increases spermatogonia and primary and secondary spermatocytes (Sanad et al., 2021b). Ginseng potentially protects against immobilization stress-induced testicular damage and fertility factors in rats (Lee et al., 2019)

Our result also showed decreasing in testosterone hormone levels and increasing in FSH and LH hormones in groups 1 and 2, which received Ciprofloxacin only, parallel to previous findings which reported that Ciprofloxacin caused impairment of Leydig cells and Sertoli cells that led to decrease testosterone level (Mokhimar et al., 2020; Zobeiri et al., 2013) but in groups 3,4and 5 which received Ginseng or vitamin-E along with Ciprofloxacin, the levels of testosterone, FSH and LH have been restored to the normal levels meaning that testicular function has been reserved. In agreement with our findings, treatment with Ginseng at 100 mg and 200 mg/kg returned FSH, LH, and testosterone to their average level (Ismail and El-Nahari, 2009). Also, treatment with Ginseng at 100 mg and 200 mg/kg doses returned FSH, LH, and testosterone to their normal levels (Shokri et al., 2015).

When comparing Ginseng and vitamin E co-administered with Ciprofloxacin, we didn't find significant differences between them regarding the previous parameters.

5. CONCLUSION

Data from the present study may indicate that Ginseng has a potential protective effect against Ciprofloxacin induced gonadotoxicity. Further studies are recommended to investigate Ginseng's protective potential from oxidative stress associated with many drugs.

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