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Article

Study of the protective effect of ginseng against testicular oxidative stress biomarkers and its gene expression induced by ciprofloxacin.

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ABSTRACT

Ciprofloxacin is the first-choice member of the fluoroquinolone antibacterials for treating testicular infections, but it may harm testicular tissue because of oxidative stress. Many mechanisms are involved, like decreasing antioxidant enzymes and suppressing gene expression. This study intends to investigate the possible protective role of ginseng against ciprofloxacin-induced testicular oxidative stress and its mechanism, if any. For this purpose, 50 adult male albino rats were randomly divided into five groups, ten rats in each group. Rats in group 1 received only ciprofloxacin at a daily dose of 156.46 mg/kg. Rats in groups 2, 3 and 4 received ciprofloxacin in a daily dose of 156.46 mg/kg, ginseng in two doses of 100 and 200 mg/kg, and vitamin E as a standard in a daily dose of 100 mg/kg, respectively. Group 5 served as control and received carboxymethylcellulose in normal saline. All these treatments were applied orally during 14 14-day experimental courses. Half the animals in each group were euthanized on day 15 from the start of the treatment, while the second half was euthanized on day 60. Both testes were dissected, immediately frozen, and evaluated for oxidative stress biomarkers and gene expression antioxidant enzymes. We found that ciprofloxacin significantly ($P \leq 0.05$) increased MDA and decreased total antioxidant capacity (TAC), superoxide dismutase (SOD) and catalase (CAT) compared to the control group. Also, the drug downregulated gene expression of SOD and CAT. Compared to all groups, the co-administration of ginseng or vitamin E with ciprofloxacin almost normalized antioxidant enzymes and upregulated the tested gene expressions. It could be concluded that ginseng ameliorates the testicular adverse effect of ciprofloxacin. So, it is highly recommended to be used as an adjunct remedy during ciprofloxacin administration for its antioxidant properties.

Keywords: Ciprofloxacin, Gene expression, Ginseng, Infertility, ROS, Testicular oxidative stress, Vitamin-E.

INTRODUCCIÓN

Reactive oxygen species (ROS) potentially contribute to male infertility [1], leading to defective sperm function, metabolism and motility [2, 3].

Oxidative stress describes when a system has imbalanced oxidation and reduction reactions leading to oxidative stress [4], which can lead to nuclear and mitochondrial DNA damage and Y chromosomal changes [5].

Former studies reported that ciprofloxacin harmfully impacted male fertility via increasing testicular oxidative stress marked by depletion in SOD (Superoxide dismutase) and GPx (glutathione peroxidase) [6-8].

Ciprofloxacin is effective in the treatment of a wide variety of infections, particularly those caused by *Gram-negative* pathogens and is considered to be the best choice for patients with complicated urinary tract infections [9], also frequently prescribed by fertility specialists in the therapy of many types of bacterial infections when leukocytospermia or before in vitro fertilization program [5].

Daily 400 mg/kg of ciprofloxacin for 7 days induced elevation in oxidative stress biomarkers [10]. Also, high doses of ciprofloxacin and enrofloxacin increase blood oxidative stress 11.
Ginseng is the most frequently used herbal medicine for immune system stimulation and as an adjuvant with prescribed drugs[12]. It is effective in the treatment of male infertility. It has been shown to induce testicular growth, increase the production of spermatozoa and testosterone levels, and sexual activity in animals [13]. Ginseng inhibits oxidative stress in rats, which lowers lipid peroxidation and increases antioxidant capacity [14].
So, we hypothesize that ginseng as an antioxidant could protect from infertility caused by oxidative stress induced by ciprofloxacin.
The adverse effect of ciprofloxacin on testicular tissue via oxidative stress has been demonstrated to achieve this objective.

MATERIALES Y MÉTODOS

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 (carboxymethylcellulose) in NS (normal saline) to a final volume of 1ml /rat dose. Ginseng was purchased with the generic name Ginsana® with a concentration of 100 mg 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 1ml /rat dose volume. Vitamin E was purchased with the 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.

Animals

Fifty 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), humidity (40-60%) and 12h/12h dark/ light cycle prior to the start of the experiment. The animals were fed laboratory formula [15] and tap water *ad libitum*.

Study design

After two weeks of adaptation to a standard diet, male rats were randomly divided into five groups, with ten in each group. Rats in group 1 received ciprofloxacin in daily doses 156.46 mg/kg[16]. Rats in groups 2, 3 and 4 received ciprofloxacin in a daily doses of 156.46 mg/kg and ginseng in two doses of 100 and 200 mg/kg[17] and vitamin E in a daily doses of 100 mg/kg, respectively. Group 5 served as control and received 1 ml carboxymethyl cellulose in normal saline. All treatments were orally administered for 14 days. Half the animals in each group were sacrificed by euthanasia using ether [18] on day 15 from the start of the treatment (1steuthanasia). In contrast, the second half was sacrificed by euthanasia [18] on day 60 from the start of the treatment (2nd euthanasia). Testis were immediately removed, frozen, and evaluated for oxidative stress biomarkers and gene expression antioxidant enzymes.

Sampling

Immediately after euthanasia, one testis from each animal was dissected, weighed and divided into two parts.

1- Testicular tissue samples for testicular oxidative stress biomarker concentrations were collected by centrifugation of the first part of the testis after homogenization with a phosphate buffer solution at pH 7.4 at 1500 xg for 5 minutes at 4° C [19]. The supernatant was taken out and preserved at -20 C. till used analysis of testicular oxidative stress markers: MDA (Malondialdehyde) concentration, SOD activity, total antioxidant capacity and CAT (catalase) activity.

2- Testicular tissue samples for testicular gene expression were collected and immediately kept at – 80°C until the expression of testicular gene expression of antioxidant enzymes was quantified. Using a Qiagen RNeasy® Mini kit, total RNA was extracted from the frozen samples following the manufacturer's protocol. RNA was determined by using Spectro star Nanodrop (BMG LABTECH®) according to the high-Capacity cDNA Reverse Transcription Kits (Applied Bio systems) protocol. Real-time polymerase chain reaction for each gene was carried out using (Quanti Tect SYBR Green PCR Kit, Qiagen), 1 µM of each forward and reverse primer for each gene (Table 1), and The real-time PCR equipment used the comparative CT method to calculate the changes in gene expression[20].

Primer	**Forward sequence**	**Reverse sequence**
B-actin	AGAAGAGCTATGAGCTGCCTGACG	CTTCTGCATCCTGTCAGCGATGC
Catalase	ACACTTTGACAGAGAGCGGA	TTTCACTGCAAACCCACGAG
GPx	GACCGACCCCAAGTACATCA	GCAGGGCTTCTATATCGGGT
SOD	GCGTCATTCACTTCGAGCAG	GGTCTCCAACATGCCTCTCT

Table 1: Primer forward and reverse sequences for gene expression analysis.

Statistical analysis

The multi-group comparisons were carried out using the one-way analysis of variance (ANOVA) technique, followed by post hoc Tukey's test for pairwise comparison at a 0.05 significance level. They were using GraphPad prism program [21].

Ethics statement

The experiment was conducted in the Departments of Pharmacology and Theriogenology, Faculty of Veterinary Medicine, Benha University, with the ethical approval number BUFVTM 090422.

RESULTADOS

Effect of ciprofloxacin alone and with ginseng or vitamin E on testicular oxidative stress biomarkers:

As shown in Figure 1, on the 15th day from the start of treatment, group 1, which was treated with ciprofloxacin, only showed a significant increase in MDA. However, adding ginseng or vitamin E normalized MDA compared to control. However, group 3, which received a high dose of ginseng, showed a significant decrease in MDA compared to the control. CAT, TAC (total antioxidant capacity) and SOD enzyme activity were reduced in the group treated with ciprofloxacin compared to the control group ($P < 0.05$). However, adding ginseng or vitamin E with ciprofloxacin normalizes CAT, TAC and SOD enzyme activity. However, the group treated with a high dose of ginseng showed a higher increase in SOD enzyme activity than group 4, which received vitamin E, and the control group, Figure 2A.

On the 60th day of treatment, all groups have been approximately returned to normal figures 1-2.

Effect of ciprofloxacin alone and with ginseng or vitamin E on antioxidant gene expression

As shown in Figure 3, on the 15th day of treatment, group 1, which received ciprofloxacin, showed significant downregulation of relative gene expression of CAT, GPx and SOD genes compared with all groups. However, supplementation of ginseng or vitamin E with ciprofloxacin approximately normalized the relative gene expression of CAT, GPx and SOD compared to the control group ($P < 0.05$). Also, group 3, which received a high dose of ginseng with ciprofloxacin, showed a higher significant upregulation of relative gene expression of CAT, GPx and SOD compared with group 2 and group 4.

On the 60th day from the start of treatment, all groups returned approximately to normal compared with the control group Figure 3.

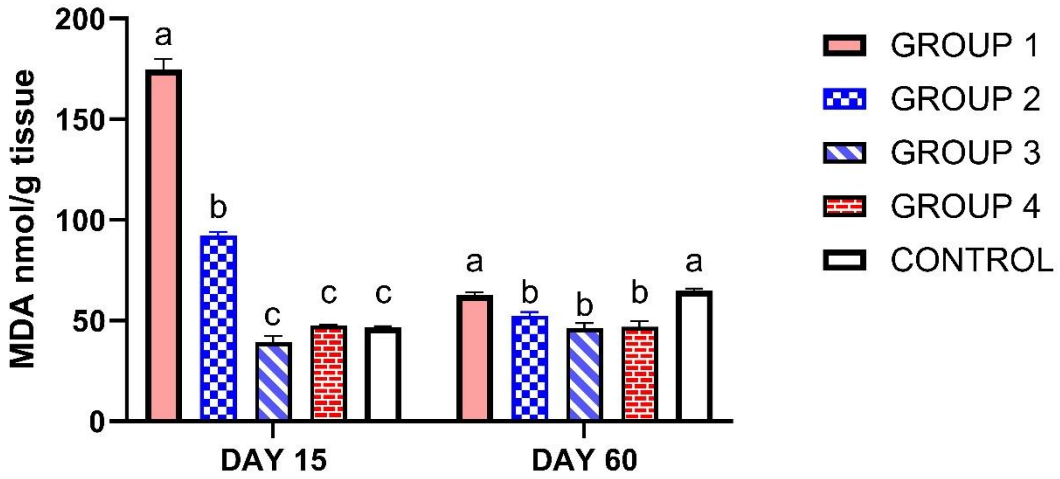

Figure 1: Influence of ciprofloxacin with or without ginseng or vitamin E administration on oxidative stress biomarker MDA obtained from rats' testis. Columns bearing different superscript letters on the same sacrifice day differ significantly at *p < 0.05* in Tukey's multiple comparison post hoc test. (Group 1) treated with ciprofloxacin only. (Group 2) Moreover, (group 3) was treated with ciprofloxacin and ginseng at a low dose and ginseng high dose. (Group 4) treated with ciprofloxacin and vitamin E. (Group 5) serve as control. MDA: Malondialdehyde.

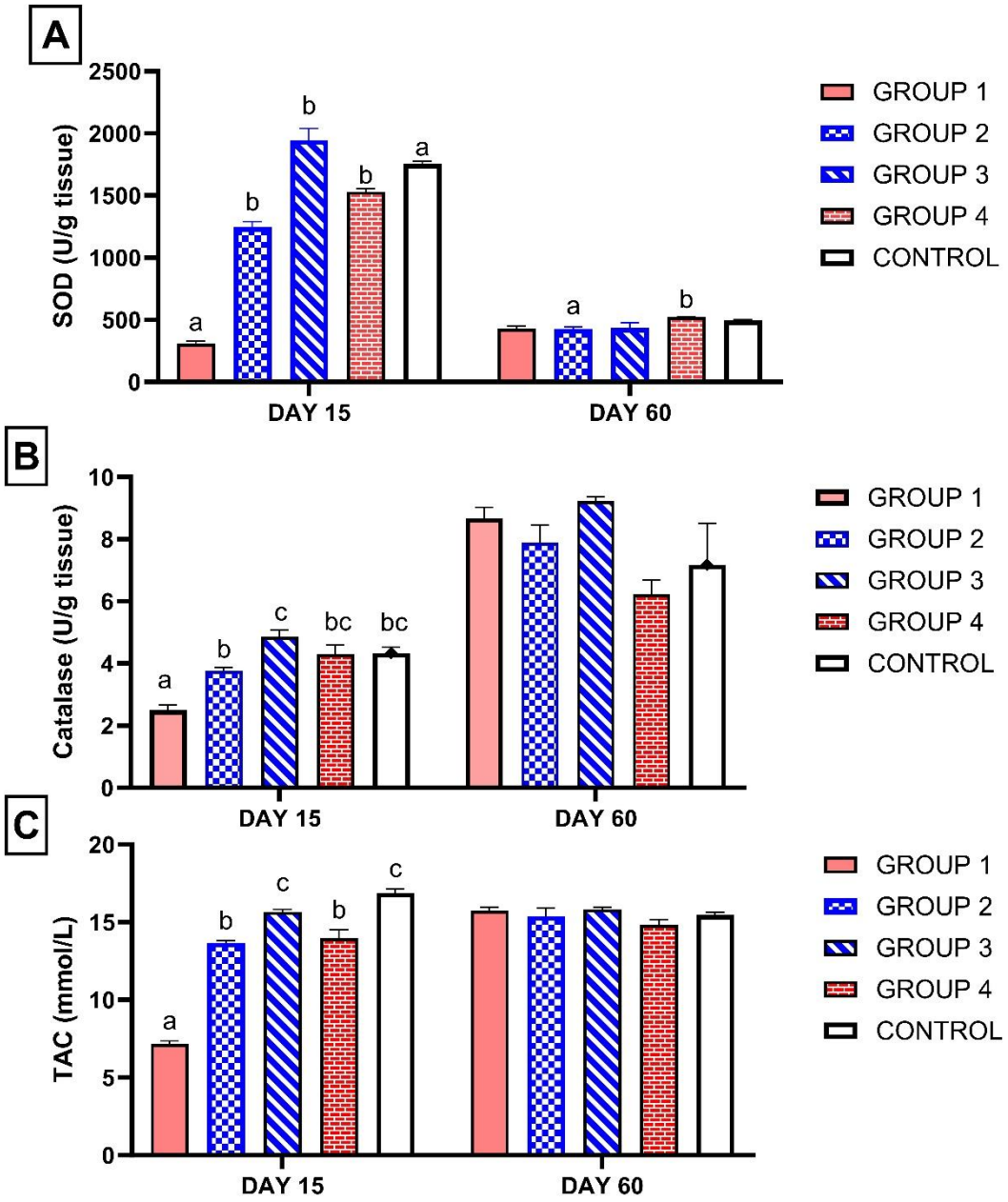

Figure 2: Influence of ciprofloxacin with or without ginseng or vitamin E administration on antioxidant enzymes SOD, Catalase, TAC obtained from rats' testis. Columns bearing different superscript letters on the same sacrifice day differ significantly at $p < 0.05$ in Tukey's multiple comparison post hoc test. (Group 1) treated with ciprofloxacin only. (Group 2) Moreover, (group 3) was treated with ciprofloxacin and ginseng at a low dose and ginseng at a high dose relatively. (Group 4) treated with ciprofloxacin and vitamin E. (Group 5) serve as control. SOD: superoxide dismutase. TAC: total antioxidant capacity.

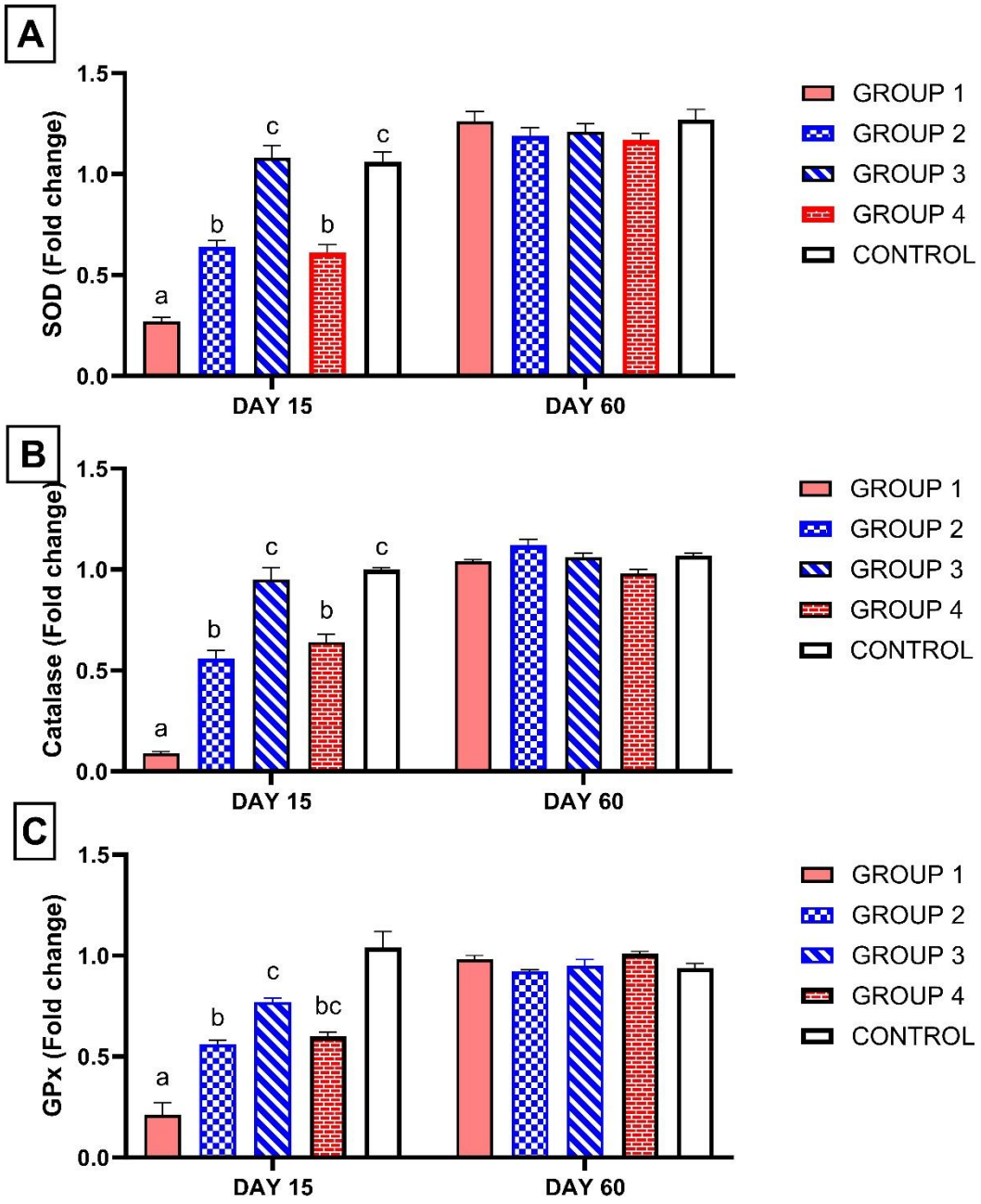

Figure 3: Influence of ciprofloxacin with or without ginseng or vitamin E administration on relative gene expression analysis of antioxidant enzymes obtained from rats' testis. Columns bearing different superscript letters on the same sacrifice day differ significantly at $p < 0.05$ in Tukey's multiple comparison post hoc test. (Group 1) treated with ciprofloxacin only. (Group 2).

Moreover, (group 3) was treated with ciprofloxacin and ginseng at a low dose ginseng high dose relatively. (Group 4) treated with ciprofloxacin and vitamin E. (Group 5) serve as control. GPx: glutathione peroxidase. SOD: superoxide dismutase.

DISCUSIÓN

The presented study is to evaluate the protective effect of ginseng against ciprofloxacin-induced oxidative stress causing male infertility. Many previous studies have demonstrated that ciprofloxacin-induced oxidative stress affects sperm parameters and function, leading to male infertility. In the present study, ciprofloxacin significantly increased MDA and decreased antioxidant enzyme activities (SOD, GPX and TAC). These

results are consistent with former reports [6-8, 22]. Ciprofloxacin is mainly related to reactive oxygen species (ROS) generation, besides metabolism-related toxicity [23]. A rise in MDA indicates testicular cell injury, accompanied by a reduction in sperm motility and sperm-oocyte fusion. [24, 25]. There are many possible mechanisms for oxidative stress causing infertility related to damage of spermatozoa because its membrane consists of polyunsaturated fatty acids, which are susceptible to lipid peroxidation [26]. Another hypothesis is that H_2O_2 can cross the membranes into the cells and inhibit the activity of some enzymes, such as G_6PD, which leads to the accumulation of oxidized and reduced glutathione, which leads to reducing the antioxidant defenses of the spermatozoa [27]. Also, oxidative stress is associated with reduced fertilization, miscarriage and congenital disabilities in the offspring due to several modifications leading to sperm DNA damage [28-30]. Ciprofloxacin also induced a significant down-regulation of antioxidant gene expression after administration of 800 mg/kg/day for 15 days [31].

We found that groups treated with ginseng in two doses showed significant improvement in testicular function via increasing antioxidant enzyme activity (SOD, TAC and GPX) but decreasing in MDA with high dose only. These findings concern previous studies [13, 14, 32, 33]. Furthermore, another study found a reduction in MDA besides an increase in SOD, CAT and GPX in rats supplemented with ginseng [34]. The ginseng root contains many amino acids, vitamins A, B2, B12, C, and E and metals like sodium, potassium, calcium, phosphorus, iodine, iron, zinc, copper and selenium [35]. This component enhanced the antioxidant protective role by decreasing MDA, the end product of lipid peroxidation and a marker for tissue damage [14]. The accumulation of MDA 36 evidenced the extensive lipid peroxidation. Also, another study reported that administering ginseng in humans for 8 weeks decreased MDA but increased SOD and CAT activities [37]. So, a decrease in MDA indicates ginseng's antioxidant activity.

SOD defends against oxygen free radicals, which are responsible for damage to the plasma membrane and biological structures, causing an elevation in the intracellular Ca2+ ion concentration leading to irreversible conversion of xanthine dehydrogenase to xanthine oxidase [38]. Also, it may be due to increasing antioxidant enzyme activities by increasing scavenger of H_2O_2, preventing the formation of free radicals [39]. So, the formation of free radicals is inhibited due to the increased activity of SOD due to ginseng administration.

Catalase and GPx are essential in detoxifying H_2O_2 [14] and indirectly protecting cells [40]. The increase in CAT activity is thought to be due to degrade H_2O_2 produced by SOD activity. Also, ginseng enhanced sex hormone levels, testicular structure, and redox status and has more antioxidant activity than Tribulus Extracts and Pollen Grains [41]. Generally, these results indicated that ginseng has protective effects against ciprofloxacin-induced oxidative stress by increasing antioxidant activity and gene expression [42]. In the same respect, another study reported that ginseng induced a protective role against alcohol-induced hepatic injury in mice by upregulating the gene expression of the antioxidant enzymes [43]. These results are also consistent with a previous study that suggested that ginseng inhibited cardiomyocyte apoptosis by inhibiting the expression of the pro-apoptotic Bax gene in rats [44].

In the present study, the group treated with ciprofloxacin beside vitamin E showed an increased antioxidant enzyme activity and upregulated its gene expression. Consistently, a study that treated 100 Parkinson's disease patients with vitamin E reported that it had a potential therapeutic target for disease-modifying treatments via activating cellular pathways involved in antioxidant and anti-inflammatory responses [45].

Furthermore, another study reported that despite ginseng 100 mg/kg/day have superior outcomes in liver protection than vitamin E 100 mg/kg/day, their antioxidant properties were similar, and this was evidenced by nearly absence of differences in liver tissue MDA, SOD or CAT levels in both treated groups [46]. Also, rats treated with vitamin E or Panax ginseng concomitant with levofloxacin significantly improve biochemical and antioxidant parameters [47].

CONCLUSIONES

Ciprofloxacin causes testicular damage by increasing the oxidative stress. However, adding ginseng or vitamin E supplementary with ciprofloxacin offers significant protection from the oxidative stress induced by ciprofloxacin treatment. So, ginseng may have a protective effect against ciprofloxacin-induced gonadotoxicity.

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