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ORIGINAL ARTICLE **OPEN ACCESS**

The Protective Effects of Naringenin on Testes Gonadotoxicity Induced by Cisplatin in Rats

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ABSTRACT
Cisplatin (CIS) is a highly effective chemotherapeutic agent for the treatment of various types of cancers but causes reproductive toxicity. The present study was aimed to investigate the protective potential of naringenin against CIS-induced testicular toxicity in rats.The fertility experiment was done on four groups of male rats. The group 1 was kept as normal control, while the group 2 and 3 were treated with intraperitoneal injection of CIS at a dose of 3 mg/kg three times per week for 35 days on 1st, 3rd and 5th days of the week. The group 2 was left as CIS-control, while the group 3 was given orally naringenin at dose of 50mg/kg for 8 consecutive weeks.Ggroup 4 was givenonly naringenin at dose of 50mg/kg orally for 8 consecutive weeks. Male fertility was evaluated by estimating serum testosterone level, epididymal sperm characters and genital organs weight. Moreover, The concentration of lipid peroxidation product (MDA) and glutathione (GSH) contents were also estimated in the testicular homogenate. Fertility parameters were further confirmed by histopathological examination of testes . The results of the present study have clearly shown that the impact of CIS on several reproductive parameters of male rats was improved by naringenin administration in term of increased serum testosterone concentration, sperm count, sperm motility and sperm viability and genital organs weight. Moreover, the present study suggested that naringenin might have a protective effect against oxidative stress-induced impaired testicular functions in CIS-treated rats as it reduced TBARS and elevated GSH levels in the testicular homogenate. Thus, the present results indicate the protective effect naringenin against CIS-induced testicular toxicity.
Keywords: *Naringenin, Cisplatin, Testicular toxicity,Antioxidant activity, Testosterone*

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INTRODUCTION

Cancer is one of the most common fatal diseases in global society. In cancer, cells divide and grow uncontrollably, forming malignant tumors, and invading nearby parts of the body. Cisplatin (CIS), a chemotherapeutic agent has been successfully used for treatment of different types of malignancies (1). It is an efficient platinum-derived alkylating agent, which acts against proliferating and resting cells (2). CIS treatment is coupled with several toxic side effects including nephrotoxicity, oxidative stress injury and testicular damage (3). Several studies suggested that CIS affects Sertoli cells and Leydig cells of testis, thereby causes anti-spermatogenic (4) and anti-steroidogenic (5) effects, respectively .

Flavonoids consist of a large group of naturally occurring compounds that are widely distributed in the plant kingdom and are found in a variety of food products, such as fruits, vegetables, nuts, seeds and beverages. Several studies have addressed the anti-oxidative, tissue-protective and tumouristatic effects of flavonoids [6,7].

Naringinis a type of bioflavonoid derived from grapefruit and related to citrus species [8]. Naringin, or its metabolite naringenin, has been reported to exhibit diverse biological and pharmacological properties, including anti-carcinogenic [9], lipid lowering [10], superoxide-scavenging [11], anti-atherogenic [12], metal-chelating[13] and antioxidant activities [14].Recently, naringin has received considerable attention asa dietary supplement, and growing evidence has indicated that naringin or naringenin displays anti-oxidant effects both in vitro and in vivo [14].In the present investigation, we have investigated the potential beneficial effects of naringenin against CIS-induced testicular toxicity in male rats.

MATERIALS AND METHODS

Chemicals

Naringenin powder was purchasedfrom Sigma–Aldrich Chemical Co., USA and Cisplatin injections (1mg/1ml vial) was purchased from the local pharmacy. The doses of cisplatin andnaringenin used in the present work were selected based onour preliminary experiments and in accordance with previous reports (15, 16).

Animals

Healthy adult male (185-200 g) and female (160-170 g) Wistar rats were used in the fertility study. Animals were obtained from Lab Animal Care Unit, Pharmacy College, PrinceSattam bin Abdulaziz University, Al-Kharj, KSA. All animals were kept under uniform and controlled conditions of temperature and light/dark (12/12 h) cycles, fed with standard rodent diet and water ad libitum. The animals were allowed to acclimatize to the laboratory condition for one week before commencement of the experiment. The experimental tests on animals have been performed in accordance with the Institutional Ethical Committee approval.

Experimental Design

Twenty-four sexually mature male Wistar rats (185-200 g b. wt) were randomly divided into four groups (n=6). Rats of the 1st group received the vehicle in a dose of 5 mL/kg and kept as normal control. The 2nd& 3rd groups were treated with single intraperitoneal injection of CIS at a dose of 3 mg/kg three times per week for 35 days on 1st, 3rd and 5th days of the week (15). In addition, the 2nd group was left as CIS-control, while the 3rdgroup was given orally naringenin at doses of 50 mg/kg for 8 consecutive week and4th group received onlynaringenin at doses of 50 mg/kg orally for 8 consecutive week. Twenty-four hours after last dose, the rats were weighed and sacrificed under light ether anesthesia.

Parameters

Estimation of testosterone and oxidative stress markers

Blood samples were collected from rats for estimations of serum levels of testosterone. Serum were separated into clean bottles, stored frozen and used within 12 h of preparation for the estimation of testosterone using ELISA kits (17). The concentration of lipid peroxidation product, MDA, was determined in homogenates of testes using the thiobarbituric acid (18). The same homogenates of testes were used in determination of the concentration of endogenous non enzymatic antioxidant, GSH (19).

Assessment of sperm motility and count :

Progressive motility was tested immediately. The right caudaepididymidis was incised and semen was squeezed on a pre-warmed slide. Two drops of warm 2.9% sodium citrate was added to semen and mixed by a cover-slip. The percentage of progressive sperm motility was evaluated visually at 400× magnification (20). Motility estimates were performed from three different fields in each sample. The mean of the three successive estimations was used as the final motility score. For sperm count, the left caudaepididymidis was incised and semen that oozed was quickly sucked into a red blood pipette to the 0.5 mark, and then diluted with warm normal saline up to the 101 mark. A drop of the semen mixture was placed on the Neubauer counting chamber and viewed under the magnification of X40 (20). The total numbers of sperm cells were counted and expressed as 10^6/mL .

Sperm viability assay (percentage of live spermatozoa)

A drop of semen was squeezed onto a clean microscope slide and mixed with 2 drops of eosin/nigrosin stain. Slides were prepared and incubated for 2 min at room temperature before being evaluated using a light microscope at ×400 magnification. Two hundred sperm were counted for each sample and viability percentages were calculated (21). Viable sperms were not stained while dead sperms stained pink.

Sperm morphological study

To determine the percentage of morphologically abnormal spermatozoa, the slides stained with eosin–nigrosin viewed under a light microscope at 400× magnifications. Two hundred sperm cells were examined per animal (Rezvanfar et al., 2008). Any disorders in the morphology and structure of either head or tail or both were considered as abnormal.

Body and sex organs weights

The initial and final body weights of the animals were recorded. The testes, seminal vesicle and ventral prostate were dissected out, freed from adherent tissues and blood, and weighed to the nearest milligram. Organ weights were reported as relative weights (organ weight/body weight ×100).

Histological analysis

Testes were carefully dissected out following abdominal incision and fixed in 10% formol-saline and processed routinely for paraffin embedding. Sections of 5 µm were obtained with rotary microtome, stained with Hematoxylin and Eosin Stalin (H/E) and observed under a light microscope.

Statistical analysis :

The values are expressed as mean ± SEM of six observations in each group. All groups were subjected to one-way analysis of variance (ANOVA), which was followed by Dunnett's post hoc test to determine the intergroup variability by using SPSS ver. 14.0. A comparison was made with the experimental control group. Differences were regarded statistically significant at the P≤ 0.05 level.

RESULTS

Blood testosterone level

The results presented in Table 1 showed that CIS significantly decreased the serum testosterone level (2.98±0.26ng/mL) as compared to normal control group (9.16±0.88ng/mL). Administration of CIS + naringeninat 50 mg/kgto rats for 8 weeks improved the level of testosterone in their blood (6.74±0.75ng/dL) when compared with that of the CIS-controls. There was no significant change in the testosterone levels in the rats treated with naringeninat 50 mg/kg alone for 8 weeks.

Testicular MDA and GSH

MDA level in the testicular tissue was found to be significantly higher in rats treated with CIS alone than those in the normal control group. GSH level in testicular tissue of rats treated with CIS alone was significantly lower than those in normal control group. The testicular MDA was significantly declined while the testicular GSH activity was significantly elevated following CIS + naringenin treatment of rats at a dose of 50 mg/kg for 8 weeks as compared with those of CIS-control rats.

Epididymal sperm characters

The average sperm count, motile sperm and viable sperm in the normal control rats were found to be 86.4±3.52millions/mL, 89.1±6.21% and 87.2±5.76%, respectively. A significant decrease in epididymal sperm count (26.4±1.92), motility (35.8±2.64%) and viability (38.9±2.73%) was observed in CIS-control rats as compared to normal controls (Table 2). Moreover, the percentage of abnormal sperms in CIS-control rats was also increased significantly (41.29±3.22%) as compared to normal controls (8.19±0.78%). Administration of naringeninat a dose of 50 mg/kg to CIS-treated rats significantly increased the sperm count (71.8±4.22%), motility (70.1±4.73) and viability (68.1±5.28) and decreased the percentage of abnormal sperms (15.11±1.33%) as compared to CIS-controls. In addition, there was no significant change in Epididymal sperm characters in naringenin (50 mg/kg) *per se* group in comparison to normal control rats.

Body and genital organs weight

Total average body weights of the rats were measured at baseline and at the completion of the experiment (8 weeks). At the end of the experiment, CIS-control rats showed high significant decrease in their body weight gain (187.6±10.46g) compared to normal control group (232.5±9.52g). The body weights of rats in CIS + naringenin (50 mg/kg) group was significantly improved compared with those in CIS-control group.

The relative weights of testes, seminal vesicles and ventral prostate of CIS-control rats were significantly lower than those of normal controls. Relative weights of testes, seminal vesicles and ventral prostate increased significantly in CIS + naringenin (50 mg/kg) group in comparison with CIS-control group. The *per se* group of naringenin (50 mg/kg) showed no significant change in the relative weights of testes, seminal vesicles and ventral prostate compared to normal control rats.

Histopathological evaluation

Histological observations of the testes of normal control rats revealed normal architecture of the seminiferous tubule (Figure 1-A). The seminiferous tubules were rounded and are separated by a thin intertubular connective tissue. The germinal epithelia are formed of normal spermatogenic layers represented by spermatogonia, primary and secondary spermatocytes, spermatids and sperms. CIS-control rats showed testicular atrophy, and degenerative changes in spermatogonia cells lining the seminiferous tubules, associated with incomplete spermatogenesis (Figure 1-B). The intercellular spacing became wider and the seminiferous tubules were shrunken and greatly depleted of germ cells. Improvement in the histopathological picture was noticed in examined sections from rats treated with CIS + naringenin (50 mg/kg) as the examined sections revealed apparent normal seminiferous tubules and interstitial spaces occupied by the Leydig cells. Most of their seminiferous tubules were close together with regular outlines and narrow interstitium (Figure 1-C).

Table 1: Effect of oral administration Naringenin for 8 weeks on blood levels of testosterone and testicular levels of TBARS and GSH of CIS-medicated male rats.

Groups	Doses (mg/kg)	Testosterone (ng/mL)	MDA (nmol /min/g tissue)	GSH (µmoles/ g tissue)
Normal Control	0.0	9.16±0.88	1.71±0.11	0.23±0.02
CIS-control	3.0	2.98±0.26[a]	6.74±0.32[a]	0.08±0.01[a]
CIS + Naringenin	3.0 + 50	6.74±0.75[b]	2.87±0.21[b]	0.17±0.02[b]
Naringenin	50	9.86±0.82[b]	1.64±0.14[b]	0.24±0.02[b]

The values are presented as means ± SEM, (n = 6).
[a] Significant differences as compared with normal control group at P < 0.05.
[b] Significant differences as compared with CIS-control group at P < 0.05.

Table 2: Effect of oral administration of Naringenin for 8 weeks on the epididymal sperm characters of CIS-medicated rats.

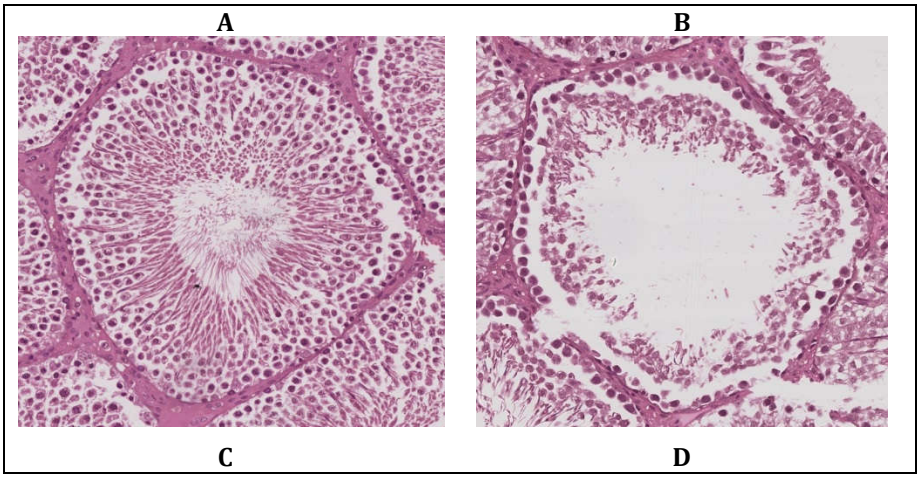
Groups	Doses (mg/kg)	Sperm count (X 10^6/mL)	Sperm motility (%)	Sperm viability (%)	Sperm abnormalities (%)
Normal control	0.0	86.4±3.52	89.1±6.21	87.2±5.76	10.19±0.78
CIS-control	3.0	26.4±1.92[a]	35.8±2.64[a]	38.9±2.73[a]	41.29±3.22[a]
CIS + Naringenin	3.0 + 50	71.8±4.22[b]	70.1±4.73[b]	68.1±5.28[b]	15.11±1.33[b]
Naringenin	50	90.1±5.72[b]	92.6±7.11[b]	84.6±7.66[b]	7.49±0.62[b]

The data are presented as means ± SEM, n = 6.
[a] Significant difference as compared with normal control group (P < 0.05).
[b] Significant difference as compared with cisplatin control group (P < 0.05).

Table 3: Effect of oral administration of Naringenin for 8 weeks on the body weight and relative weight of reproductive organs of CIS-medicated male rats.

Groups	Doses (mg/kg)	Initial b.wt (g)	Final b.wt (g)	Relative weight of reproductive organs (g/100 g b.wt)		
				Testes (Pair)	Seminal vesicles	Ventral prostate
Normal control	0.0	182.2±7.73	232.5±9.52	1.82±0.11	0.72±0.05	0.57±0.04
CIS-control	3.0	185.2±8.25	187.6±10.46[a]	0.59±0.05[a]	0.25±0.03[a]	0.22±0.01[a]
CIS + Naringenin	3.0 + 50	192±8.11	225.4±11.32[b]	1.47±0.08[b]	0.55±0.05[b]	0.39±0.04[b]
Naringenin	50	183±7.93	235.2±8.69[b]	1.79±0.11[b]	0.66±0.03[b]	0.55±0.06[b]

The values are presented as means ± SEM, (n = 6).
[a] Significant differences as compared with normal control group at P < 0.05.
[b] Significant differences as compared with diabetic control group at P < 0.05.



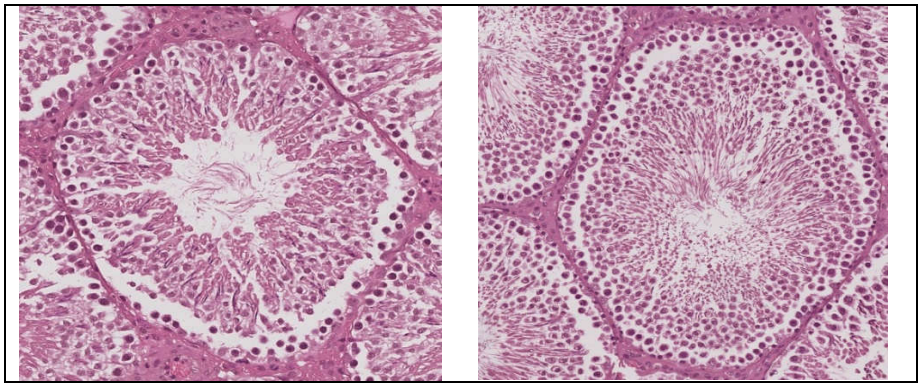


Figure 1: Photomicrograph of testicular histology of the (A) Control rats showing normal seminiferous tubules and normal structure of germinal epithelium. (B) CIS-control rats, showing atrophic and degenerated seminiferous tubules associated with incomplete spermatogenesis and sloughing of degenerated germ cells. (C) CIS + Naringenin at a dose of 50 mg/kg restored the degenerative changes in the seminiferous tubules towards normality. (D) Naringenin aloneat a dose of 50 mg/kg showing no change in seminiferous tubules and germinal epithelium compared to normal control (X 400).

DISCUSSION

The present investigation demonstrated the protective potential of naringenin against CIS induced testicular damage. Many recent reports have shown that CIS therapy induces oxidative stress in testicular tissues (15). CIS causes lipid peroxidation and decreases the activity of enzymes that protect against oxidative damage in testicular tissue of CIS-treated rats. The present study showed that CIS lead to an increased oxidative stress in testes, which was manifested by an increase in MDA level and decrease in antioxidant GSH. The level of tissue MDA is reported to be a reliable marker of lipid peroxidation (22). The present observation is in agreement with previous findings showing an increase in renal MDA level and decrease in the testicular antioxidant activity of GSH in CIS-medicated rats (23).

Exogenous protective agents with antioxidant properties were reported to show some protective effects against CIS-induced toxicity. Bioflavonoids are promising agents against various toxicities associated with oxidative stress. In the current study, naringenin ameliorated CIS toxicity, indicated by significant reduction in the elevated MDA and increase testicular GSH level. These results were confirmed by the histopathological examinations. Previous studies indicated that naringenin (11-14) have potent antioxidant activity. Furthermore, Conklin (2004) mentioned that using of antioxidants during cancer chemotherapy may enhance therapy by reducing the generation of oxidative-stress (24). Accordingly, naringenin could possibly have a testicular protective effect in CIS-treated rats by exerting its beneficial effect via modulating the antioxidant system. The reports (13,14) indicating that the naringin and naringenin have potent antioxidant activity supports these findings.

The study of Maines (25) demonstrated that exposure to CIS, lowered serum testosterone levels in rats. One of the molecular mechanisms of anti-gonadal effects induced by CIS is by mediating dysfunction of biosynthesis of testosterone (26). In the current study, serum testosterone levels were significantly reduced in CIS-treated rats compared to normal controls. Cao et al. (2004) indicated that excessive oxidative stress reduced levels of key enzymatic and non-enzymatic antioxidants in Leydig cells, and resulted in decline in testosterone secretion (27). Accordingly, the reduced serum testosterone level in CIS-treated rats in our study could be attributed to the impairment of Leydig cells. The administration of naringenin 50 mg/kg caused a significant increase in testosterone level in serum of CIS treated male rats. These results are in agreement with the earlier findings (28) indicating that naringenin increases the plasma levels of testosterone in diabetic male rats.

Gonadal dysfunction and decrease in testosterone production are the consequence of cancer chemotherapeutic agents (29). In our study, the reduction in epididymal sperm motility and count in CIS-control rats could be connected to the reduction in the serum testosterone level. We concurred in this matter with Gong and Han (30) who explained that lowering of epididymal sperm motility and count suggested an undersupply of testosterone to the epididymis. Besides hormonal alteration, the spermatogenic inhibition may also be due to the generation of ROS by CIS in the testicular tissue and the consequential elimination of sperm cells at different stages of development (31).

Our results showed that all the sperm parameters were recovered after treatment with naringenin (50 mg/kg). The improvement that observed in spermatogenesis among naringenin treated rats may be associated with the antioxidant properties of naringenin. This result may suggest that naringenin could have an effect on spermiogenesis process and they could favor normal sperm production. Additionally,

testosterone deficiency (like that observed in our CIS-control rats) produces immature sperm by early sloughing of spermatids from the Sertoli cells (32). The improvement in percentages of sperm abnormality and viability, in the present study, coincided with the increased testosterone level in the serum of naringenin-treated rats.

The weights of testes and accessory sex organs are sensitive end points that can be used in evaluation of negative effect on male reproduction (33). In the present study, there was a significant decrease in the weights of testes and the accessory reproductive glands in CIS-control rats compared to the normal controls. This suggests that testis and accessory sex organs are vulnerable targets to CIS in rats. Reductions of testicular and accessory sex organs weights in CIS-control animals, shown in this study, have already been described by Malarvizhi and Mathur (34) and can be related to the reduced level of testosterone. Accordingly, the significant increase in the reproductive organ weights of rats that treated with CIS + naringenin (50 mg/kg) may be attributed to the improvement in testosterone levels. This effect can be explained also by the anti-oxidant property of naringenin that prevents cellular damage occurring as a result of oxidative stress in spermatogenic cells of seminiferous tubules and Leydig cells of the testes.

From the above results, we conclude that CIS treatment has a deleterious impact on fertility of male rats and oral administration of naringenin has a protective effect against testicular damage induced by CIS. Based on our data, it is suggested that naringenin may be a therapeutic agent in the treatment of CIS induced testes gonadotoxicity.

CONFLICT OF INTEREST STATEMENT

We declare that we have no conflict of interest.

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