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Abrogation by Curcumin on Testicular Toxicity Induced by Cisplatin in Rats

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Abstract Cisplatin is one of the most effective and widely-used antineoplastic agents for the treatment of testicular germ cell tumors. The present study was conducted to examine the possible modifying effects of curcumin against testicular toxicity induced by cisplatin in male rats. 60 male albino rats were equally divided into six groups; the first and second groups were the control and curcumin treated group respectively while the 3rd group was cisplatin treated group; the 4th and 5th groups were co- and post treated cisplatin rat with curcumin respectively and the 6th group was self treated cisplatin rat group. Many side effects were observed in animals injected with cisplatin such as loosing of body weight, loss of activity, weakness, yellowish body hair. A significant decrease in the body and testicular weights,, sperm counts, sperm motility, plasma testosterone, luteinizing hormone reduced glutathione, total antioxidant capacity, and total protein levels in cisplatin and cisplatin self treated groups when compared with the control group. On the other hand; a significant increase in the MDA and NO in cisplatin and cisplatin self treated groups when compared with the control group. sperm count and sperm motility, GSH and TAC exhibited significant increased in cisplatin treated with curcumin when compared with cisplatin groups, moreover, sperm abnormality, MDA, NO and total protein exhibited significant decrease in cisplatin treated groups with curcumin when compared with cisplatin groups. A significant decrease in sperm abnormality, MDA, NO and total protein and a significant increase in GSH and TAC in Co-treated group when compared with post treated cisplatin with curcumin. Our recommendation, administration of curcumin caused ameliorative effect against cisplatin-induced testicular toxicity.

Keywords: *cisplatin, curcumin, testis, reproductive hormones, oxidative stress*

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1. Introduction

The testis is known target organ for injury resulting from exposure to both chemotherapeutic and toxics environmental agents. Cisplatin has been used as a key chemotherapeutic agent for many types of malignant tumors. It is standard treatment of testicular cancer and is also effective for ovarian, bladder, cervical, head, neck, esophageal and small-cell lung cancer [1,2,3]. The major cytotoxic action of cisplatin to eradicate malignant tumors, is to intercalate the DNA backbone of rapidly growing cells and interfere with cell division [4,5]. However, its dose related side effects, chiefly production of reactive oxygen species and induction of cell apoptosis could adversely damage non target tissues that are not the goal of treatment [6]. Curcumin, a widely used spice and colouring agent in food, Curcumin has been claimed to be a potential anti-inflammatory agent with phyto-nutrient and bio-protective properties [7]. Curcumin has also shown to alleviate various forms of male reproductive disorders in experimental animals and thus to enhance fertility [8,9,10]. Curcumin was shown to be a potent scavenger of a variety of reactive oxygen species including hydroxyl radicals, nitrogen dioxide radicals, and superoxideadicals [11,12]. Based on these evidences, the present study was conducted to examine the possible modifying effects of curcumin against testicular toxicity induced by cisplatin in male rats.

2. Materials and Methods

The experiments were performed on 60 male albino rats weighing 110 ±10 g and of 9 week's age. They were obtained from our laboratory farms, Zoology Department, Faculty of Science, Tanta University, Egypt. The rats were kept in the laboratory for one week before the experimental work and maintained on a standard rodent diet (20% casein, 15% corn oil, 55% corn starch, 5% salt mixture and 5% vitaminzed starch; Egyptian Company of Oils and Soap Kafr-Elzayat Egypt) and water available *ad libitum*. The temperature in the animal room was maintained at 23±2°C with a relative humidity of 55±5%. Light was on a 12:12 hr light -dark cycle. The experimental protocol was approved by Local Ethics Committee and Animals Research. Sixty rats were equally divided into six groups (10 animals each).

G_1; Control group in which animals did not received any treatment.

G_2; Curcumin group in which animals received curcumin (50 mg/Kg body weight/ day) (Sigma chemical Co, Germany) orally by stomach tube for four weeks according to Choudhary et al. [13].

G_3; Cisplatin rats group in which rats were injected intraperitoneally with Cisplatin (4 mg /kg body weight/ twice a week) (Unistin 50 ml/50 mg vial Eimc united Pharmaceutical Badr City, Cairo, Egypt) for four weeks according to Sanchez-Gonzalez et al. [14].

G_4; Co-treated group in which animals were injected intraperitoneally with cisplatin plus received orally curcumin for four weeks.

G_5; Post treated group in which animals were injected intraperitoneally with cisplatin for four weeks and then treated orally with curcumin for another four weeks.

G_6; Self treated rat group in which rats were injected intraperitoneally with cisplatin for four weeks and left for another four weeks without receiving any treatment.

At the end of the experimental period, rats were fasted overnight and for clinical chemistry. Rats were weighed and euthanized with intravenous injection with sodium pentobarbital and subjected to a complete necropsy. Blood samples were individually collected from the inferior vena cava of each rat in non heparinized glass tubes to estimate blood parameters. Testes and epididymides were carefully removed, cleaned from adhering connective tissue in cold saline and weighed. Testes were quickly stored at -80°C until homogenization for biochemical analysis. On the other hand, epididymides were prepared for fertility evaluation (sperm count, motility and morphology) according to Seed et al. [15]. The number of sperms was calculated according to Cheng et al. [16]. Blood serum was separated by centrifugation at 3000 rpm for 15 minutes. Blood serum was analyzed to determine the total testosterone (TT) according to Abraham et al. [17], while follicle stimulating hormone (FSH) and plasma luteinizing hormone (LH) were estimated according to Taylor et al. [18]. A 10 % (w/v) homogenate of testis was prepared in ice-cold normal saline using a chilled glass-teflon porter-Elvehjem tissue grinder tube, and then centrifuged at 3000 rpm for 15 min. The supernatant was used for estimation TAC by colorimetric method according to Koracevic et al. [19], total protein concentration according to Bradford [20], malondialdehyde (MDA) according to Satoh [21], glutathione reduced glutathione (GSH) according to Beutler et al. [22] and nitric oxide (NO) activity was done according to the method according to Montgomery and Dymock [23].

Results were analyzed using one-way analysis of variance (ANOVA) followed by the Least Significant Difference (LSD) tests to compare between different groups. Data were presented as the mean±SEM. P values less than 0.05 were considered significant. All statistical analyses were performed using SPSS statistical version 16 software package (SPSS® Inc., USA).

3. Results

Various side effects were observed in animals injected with cisplatin such as loosing of body weight, loss of activity, weakness, yellowish body hair and 15±3.2% mortality was recorded in cisplatin group. About 20±2.6% mortality was recorded in self treated cisplatin group, on the other hand, while 18±2.5% mortality was recorded in post treated cisplatin with curcumin group.

Figure 1 showed that a significant decrease in testosterone, LH and FSH in cisplatin when compared with control and curcumin groups. However, curcumin ameliorated the cisplatin-reduced serum level of sexual hormones including testosterone, LH and FSH a significant increased in LH, FSH and testosterone in co- and post treated rats with curcumin groups when compared with cisplatin and self treated groups. On the other hand, significant increased LH and testosterone in Co-treated group when compared with post treated cisplatin with curcumin (Figure 1). For FSH there is no significance changed between self and cisplatin group (Figure 1).

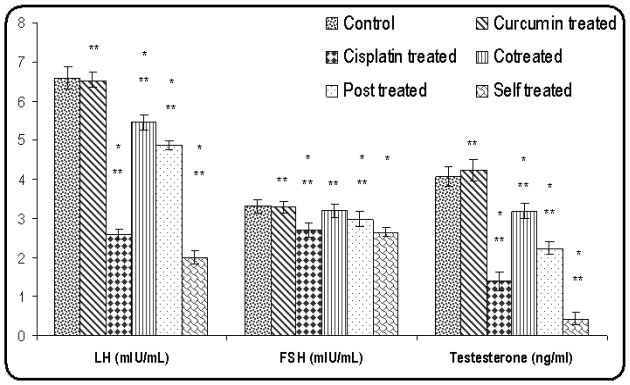

Figure 1. Changes in the serum LH (mIU/mL), FSH (mIU/mL) and testesterone (ng/dL) levels in the different groups under study. Data are expressed as mean ± S.E.M. * = *sig. with control group* **= *sig. with Cisplatin treated group*

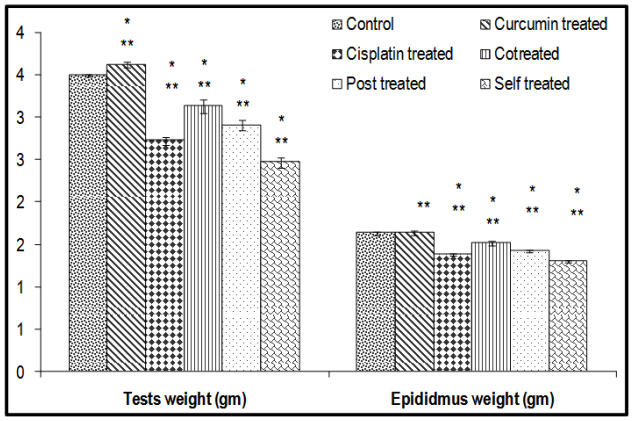

Figure 2. Changes in the testis and epididmus weight in the different groups under study**.** Data are expressed as mean ± S.E.M. * = *sig. with control group* **= *sig. with Cisplatin treated group*

Administration of cisplatin alone significantly reduced body, testes and epididmus weights weight as compared to control animals. while, administration of curcumin along with cisplatin restored testes and epididmus weights to normal. self-treated some recovery of epididymal and testicular weigh than cisplatin group (Figure 2). Figure 3 showed that sperm counts and sperm motility exhibited significant decrease in cisplatin group when compared with control or curcumin groups. Meanwhile, sperm abnormality exhibited significant decrease in cisplatin group when compared with control or curcumin groups.

Also, Figure 3 showed that sperm count and sperm motility exhibited significant increased in treatment with curcumin when compared with cisplatin and cisplatin self treated groups. On the other hand, significant increase in sperm count and sperm motility in Co-treated group when compared with post treated cisplatin with curcumin. Three different abnormalities in sperm morphology were found with a higher percentage in cisplatin and cisplatin self treated groups than control or curcumin groups. These abnormalities were bent tail, bent neck and banana head sperms (Figure 3). Sperm abnormality exhibited significant decrease in treated groups with curcumin when compared with cisplatin and cisplatin self treated groups (Figure 3). Also, significant decrease in sperm abnormality in Co-treated group when compared with post treated cisplatin with curcumin.

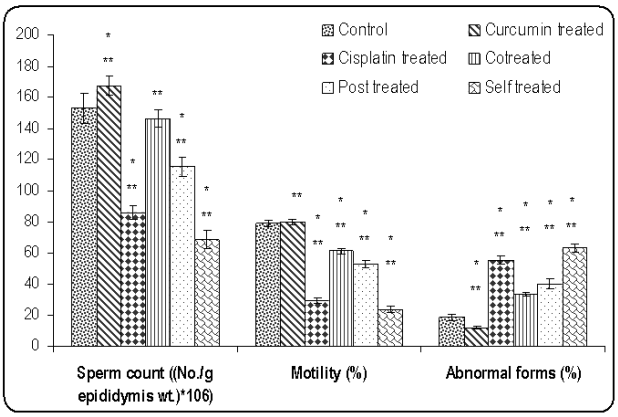

Figure 3. Changes in the sperm counts, motility and abnormality in the different groups under study. Data are expressed as mean ± S.E.M. * = *sig. with control group* **= *sig. with Cisplatin treated group*

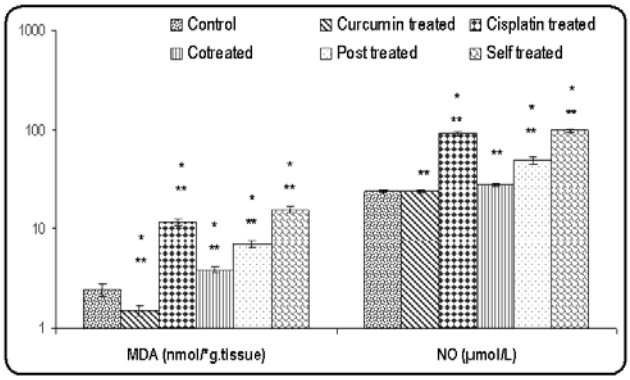

Figure 4. Changes in the **MDA (mmol/g. tissue) and NO (µmol/L)** levels in the different groups under study. Data are expressed as mean ± S.E.M * = sig. with control group **= sig. with Cisplatin treated group

Figure 5 showed that a significant increase in MDA, NO and total protein in cisplatin and self treated groups when compared with control and curcumin groups. A significant decrease in MDA, NO and total protein in Co- and post treated rats with curcumin groups when compared with cisplatin and self treated groups while, a significant increase in GSH and TAC in Co- and post treated rats with curcumin groups when compared with cisplatin and self treated groups (Figure 4 & Figure 5). On the other hand, a significant decrease in MDA, NO and total protein in Co-treated rats with curcumin groups when compared with and post treated rats with curcumin groups while, a significant increase in GSH and TAC in Co-treated rats with curcumin groups when compared with and post treated rats with curcumin groups. However, a significant decreased in GSH and TAC in cisplatin and self treated groups when compared with control and curcumin groups (Figure 4).

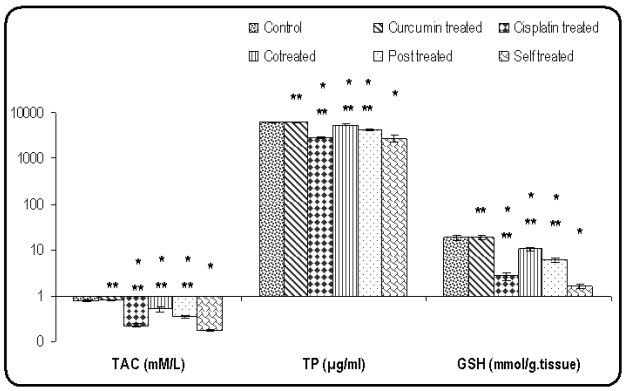

Figure 5. Changes in the TAC (mM/L), total protein (µg/ml) and GSH (mmol/g. tissue) levels in the different groups under study. Data are expressed as mean ± S.E.M. * = sig. with control group **= sig. with Cisplatin treated group

4. Discussion

A little is known about herbal plants as protective agents against cisplatin-induced testicular toxicity. Cisplatin is one of the leading anticancer drugs in the chemotherapy treatment of variety of cancer types [24,25]. The major cytotoxic action of cisplatin to eradicate malignant tumors, is to intercalate the DNA backbone of rapidly growing cells and interfere with cell division [26]. Recently, much attention has been focused on the protective effects of antioxidants and naturally-occurring substances against cisplatin-induced nephrotoxicity [27,28]. However, little is known about herbal plants as protective agents against cisplatin-induced testicular toxicity. This study was designed to examine the possible modifying effects of curcumin against reproductive disorders induced by cisplatin in male albino rats. The current study shows a significant The hormonal assays revealed that the cisplatin injection resulted in a significant reduction of testosterone TT, LH and FSH in cisplatin and self-treated groups while, in curcumin treated groups, it restore the decrease in this hormones. This remarkable reduction of sexual hormones which were found in the current study might be explained by severe damages, which cisplatin exerted on leydig and sertoli cells by increased generation of free radicals is one of the possible mechanisms involved in cisplatin-induced Leydig cell degeneration. Decrease in level of testosterone confirming other studies [29,30]. Besides, the cisplatin administration in a relatively long term may be result in resulted in suppression of upper axis (hypophysis-testis) and the reduction of both testosterone and did not up regulate the LH and FSH release. This finding is in line with that of Pogach et al. [31] who observed that treating adult rats with cisplatin results in detrimental effects on pituitary –testicular axis the effects were manifested by decrease on level of testosterone and luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Injection of cisplatin induced a marked inhibition of sperm motility.

This result are supported by the finding of **Atessahin et al.** [32] who concluded that the toxic effects induced by cisplatin administration include a decrease in sperm concentrations, a reduction in sperm motility, an increase in abnormal sperm ratios. Poor sperm motility may be associated with OS and DNA fragmentation this results agree with **Silici et al.** [33]. As Sperm damage induced with cisplatin has been reported to be associated with oxidative stress. Thus, the combination of curcumin delivery together with a potent antioxidant may be the appropriate approach to reduce the toxic side effect of cisplatin death and the toxic. In the present study, showed significant increases in MDA content of testicular tissues in rats treated with cisplatin. This elevation in testicular MDA levels compared with the control group. **Rezvanfar et al.** [34] reported that the increased in lipid peroxidation is one of the toxic manifestations of cisplatin administration in testis. **Waseem and Parvez** [35] reported that Pre-treatment of rat with CMN significantly restored the mitochondrial lipid peroxidation levels and CMN should be investigated as a potential safe and remarkable approach in attenuating the adverse effects induced by CP-related toxicants. The present study indicates the marked elevation in NO level in the damaged testicular tissue of the cisplatin-treated rats this results agree with **Keshtmand et al.** [36]. This elevation of NO generation in the testicular tissue of cisplatin-treated rats supports the above mentioned mechanism relating generation of NO caused by free radicals under oxidative stress. The present study demonstrated that, Co-administration of curcumin attenuated the adverse effects of cisplatin in rats by reducing the elevated level of NO. Confirming this finding, **Ilbey et al.** [8] reported that co-administration of CMN with CIS reduced the increase of iNOS expression in the testicular tissue of cisplatin-treated rats. The measurement of GSH in biological samples is essential for the evaluation of the redox and detoxification status of cells and tissues in relation to the protective role of GSH against oxidative and free-radical-mediated cell injury [37]. **Kandemir et al.** [38] reported that the administration of cisplatin resulted in a significant reduction in testis GSH were prevented by curcumin compared to the cisplatin alone group. Total antioxidant capacity (TAC) considers the cumulative effect of all antioxidants [39]. The decrease in TAC levels, this is probably due to the depletion of the antioxidant molecules as they are consumed in the process of protecting cells against ROS generated by cisplatin this result agree with the previously reported studies of **Anand et al.** [40] who reported that cisplatin injection resulted in decline in TAC in rat testes. Testicular protein indices of functional capacity of the testes. Protein content of testicular tissue is considered as a marker of tissue injury, damage and rewound healing [41]. Testicular proteins are required for spermatogenesis and sperm maturation [42]. Thus, the significant reduction in the concentration of testicular protein in cisplatin could impair sperm maturation [43]. The restoration of the concentration of testicular protein following the administration of the aqueous curcumin could enhance sperm maturation, indicating the androgenic potential of the plant. The significant reduction in the testicular total agree with previous studies of **Kamel et al.** [44]. Curcumin has proved its credentials as a wonderful chemopreventive agent against a variety of cancers. Oral combination with curcumin could effectively counteract cisplatin-induced oxidative induced testicular dysfunction as represented through ameolerating all oxidative stress and improving anti-oxidant defense system and prevent all toxic effect of cisplatin.

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