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β-sitosterol protects against cisplatin-induced nephrotoxicity through amelioration of oxidative stress in rats

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Abstract

Kidney damage is a major concern related with Anti-malignancy drugs. It is well established that overproduction of reactive oxygen species plays vital role in progress of the pathogenesis of nephrotoxicity. The aim of this study is investigated the modulatory effect β-sitosterol (BT) on cisplatin (CP) that induced nephrotoxicity by targeting oxidative stress and biochemical parameters for kidney function markers in rats. Following a single dose of cisplatin (CP) an intraperitoneal (7.5 mg/kg BW) at seventh day group II,III and β-sitosterol (BT) 5 ml/kg was administered for 10 days group I,III, IV, after decapitation of the rats, trunk blood was obtained, and the kidney tissue was removed for the measurement of xanthine oxidase, lipid peroxidation, (H_2O_2) generation and antioxidant enzymes, like, catalase, glutathione reductase and glutathione peroxidase kidney function markers like serum creatinine and BUN, further examination for histopathological changes. Cisplatin (CP) administration group was increased the glutathione depletion, xanthine oxidase and lipid peroxidation activity and decrease in (glutathione reductase, catalase and glutathione peroxidase) and phase-II detoxifying (quinone reductase and glutathione-S- transferase) enzymes activities significantly ($p<0.05$) when compared with the control, histological findings provide same the protective effects of β-sitosterol (BT) against cisplatin (CP) induced acute nephrotoxicity. In conclusions; the current study revealed β-sitosterol (BT), through its antioxidant actions, alleviates cisplatin-induced oxidative damage, which suggests that β-sitosterol (BT) may be of therapeutic benefit when used with cisplatin.

Keywords: β-sitosterol; kidney; cisplatin; oxidative stress

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Introduction

Cisplatin (CP) is chemotherapeutic drugs that used as treatment of several of genitourinary cancers like, testicular, ovarian and bladder cancers [1]. Active metabolites of (CP) interferes with DNA replication, which kills the fastest proliferating cells, DNA and RNA synthesis through inhibits DNA synthesis; cross-linking; guanine N7 site which is eventually lead to arrested cellular homeostasis [2,3]. Cisplatin (CP) not only targets cancer cells

but also normal proliferating cells caused down regulation of normal cell proliferation, genomic instability, overproduction of different reactive toxic moieties and necrosis [4]. Cisplatin (CP) induced hepatotoxicity is a complex process characterized by direct damage to major cellular macromolecules, generation of reactive oxygen species (ROS) [5, 6]. in spite of endogenous antioxidant systems such catalase (CAT), glutathione peroxidase (GPx) and superoxide dismutase (SOD) can prevent toxic and damage effects of (ROS) however, overcome reactive oxygen species may be resulting from cisplatin, a natural antioxidant defences of liver cells and lead to inhibition of the lipid peroxidation and prevention hepatotoxicity [7, 8]. The exact etiopathogenesis of kidney damage is not well elucidated but the impact of oxidative stress has been well documented in toxic manifestations and disease pathphysiology caused by antineoplastic medicine [9,10]. Exaggerated reproduction of reactive oxygen species ROS by antineoplastic medicine causes change of cellular big molecules resulting in inhibit activity of the regulators of normal cellular function [11, 12]. Although use of antineopalstic drugs for the treatment of cancer patients commonly approach is associated with adverse side effects [12]. This study is an attempt to address the issue of nephrotoxicity accompany antineoplastic drugs, attention has been given to combination therapy with natural or synthetic agents, such as antioxidants, plant derived compounds [13,14]. β-sitosterol (BT) is a well-known lipid-soluble cellular antioxidant and free-radical scavenger which protects cellular integrity from various toxic moieties. Importance of (BT) for proper cellular and biological functioning makes it an essential nutrient [15,16]. The biological functions of β-sitosterol including antioxidant, antidiabetic and hepatoprotective efficacies have been reported [17,18]. β-sitosterol have antioxidant, chemopreventive and chemotherapeutic effective in different cancer types [19]. β-sitosterol has many reports have noted that it an anti-inflammatory and anti-carcinogenic agent during promotion/progression stage of colon cancer [20]. Various preclinical and clinical findings demonstrate that β-sitosterol (BT) has strong extenuative potential against the pathogenesis of various human diseases [21]. In this paper, we explore the possibility to investigate the modulatory action of β-sitosterol (BT) on cisplatin (CP) induced nephrotoxicity in rats by analyzing biochemical and histological parameters.

Materials & Methods

Experimental design

Twenty mature male rats have (6-8) weeks old and have weight (150-200 gram) were

taken from Kufa University, Veterinary college, the male Rats were housed at temperature (25 ^{0}C) and (12) hour light/ (12) dark cycles and were supply by pellet diet with pure water. Before starting by the treatment, the rats were left at normal climate for (7) days. The animals parted randomly to four group, each group consist from five animals, the effective of treatment by β-sitosterol on oxidative stress that induce by Cisplatin s and nephrotoxicity responses in the kidney, the four groups were placed in many of the cages and provide several doses as:

Group I (Control group) administrated normal saline from days once for 10 days. Group II was given a cisplatin (one injection) (7.5 mg/kg/BW-intraperitoneally) at day of seventh according to Rehman *et al* [22]. Groups IV received β-sitosterol (5 ml/kg) administrated orally body weight daily one dose each 10 day according to Malini *et al* [23]. Group III received both cisplatin (CP) and β-sitosterol (BT) treatments as previously indicated.

Preparation of subcellular fluid

According to Ayako and Fridovich, 2002 [24] distilled water contains Kidney tissues even it become pink color. glass tissue grinder uses to homogenized theses tissue then adding sucrose (0.88 M) and washing and re-suspension then cooled ultracentrifuge was use for homogenates were fractionated for obtaining subcellular fluid according to methods of [24].

Estimation of MDA formation

According to Wright et al. [25] the lipid peroxidation was prepared.

Assay for glutathione-S-transferase activity

According to [26] the Glutathione-S-transferase was prepared.

Estimation of reduced glutathione

According to [27] The GSH in kidney was done.

Glutathione reductase activity assay

Estimated depend on the method of [28].

Catalase activity assay

Catalase activity was measured by the method of [29].

Xanthine oxidase activity assay

The activity of xanthine oxidase was estimated by the method of Stripe and Della Corte [30].

LDH activity

Estimated by in serum according to the method of [31].

Quinone reductase activity assay

According to Benson et al. [32] the quinone reductase was estimated.

Creatinine level

According to Hare [33] Creatinine was done preparation.

Blood urea nitrogen (BUN) level

According to Kanter [34] was preparing BUN.

Protein estimation

Concentration of the protein all the samples was estimate depend on Lowry et al. [35].

Histological investigation

In histopathlological change of the kidney tissue placed and fixed in (10%) buffered formalin solution at 48^{0}C as [36].

Statistical analysis

All groups are submitted to applying the mean ± standard error. The Differences significance among the groups, where analyzed by (ANOVA) test and submitted to comparisons of minimum criterion and tukey–Kramer multiple test at ($p < 0.05$) [37].

Results

Table 1

Results of pretreatment of β-sitosterol on GR, GST and GSH on cisplatin induced renal redox imbalance.

Treatment groups	GSH (nmol GSH/g tissue)	GST (nmol CDNB conjugate formed/ min/mg protein)	GR (nmol NADPH oxidized/min/ mg protein)
Group I vehicle only	0.35 ± 0.03	121.4 ± 1.90	205.3 ± 2.61
Group II cisplatin only	0.20 ± 0.01###	71.32 ± 2.35***	117.1 ± 2.11***
Group III β-sitosterol + cisplatin	0.33 ± 0.05***	86.41 ± 7.3##	143.4 ± 2.61#
Group IV β-sitosterol only	0.38 ± 0.04	124.3 ± 3.20	187.4 ± 7.51

The data represent, mean ± SE, each group consist from (5) animals, there are significant difference with group (1) (***P<0.002). There are significant differences from cisplatin treated group (# P<0.03 and ## P<0.004). β-sitosterol (5) mg/kg, body weight.

Table 2

Results of pretreatment of β-sitosterol on Xanthine Oxidase, Catalase, and Lactate dehydrogenase on cisplatin induced renal redox imbalance.

Treatment groups	Catalase (nmol H_2O_2 consumed/ min/mg protein)	XO (lg uric acid/min/mg protein)	LDH (nmol NADH oxidized/min/mg protein)
Group I vehicle only	35.56 ± 1.23	0.405 ± 0.013	211.4 ± 16.31
Group II cisplatin only	21.30 ± 1.30***	0.656 ± 0.12***	349.50 ± 7.31***
Group III β-sitosterol + cisplatin	31.24 ± 3.11###	0.467 ± 0.027##	269.41 ± 22.34##
Group IV β-sitosterol only	36.71 ± 2.32	0.403 ± 0.035	193.1 ± 7.1

The data represent, mean ± SE of each group consist from (5) animals. There is significant difference with group (1) (**P<0.03). There is significant difference from cisplatin treated group (#P<0.004 and ##P<0.001).

Table 3

Results of pretreatment of β-sitosterol on Quinone Reductase, Creatinine and BUN on cisplatin induced renal redox imbalance.

Treatment groups	QR (nmol NADPH oxidized/min/mg protein)	Creatinine (mg/100 ml) IU/l	BUN (mg/100 ml) IU/l
Group I vehicle only	251.6 ± 5.11	1.784 ± 0.11	34.91 ± 2.32
Group II cisplatin only	122.8 ± 31.72***	2.871 ± 2.37***	44.37 ± 2.84***
Group III β-sitosterol + cisplatin	182.7 ± 41.26###	1.981 ± 0.28##	38.78 ± 1.13##
Group IV β-sitosterol only	259.4 ± 3.94	1.773 ± 0.41	36.82 ± 3.53

The data represent, mean ± SE of each group consist from (5) animals. There is significant difference with group (1) (**P<0.004). There is significant difference from cisplatin treated group ($^{\#}$P<0.03 and $^{\#\#}$P<0.005). β-sitosterol 5 mg/kg. b wt.

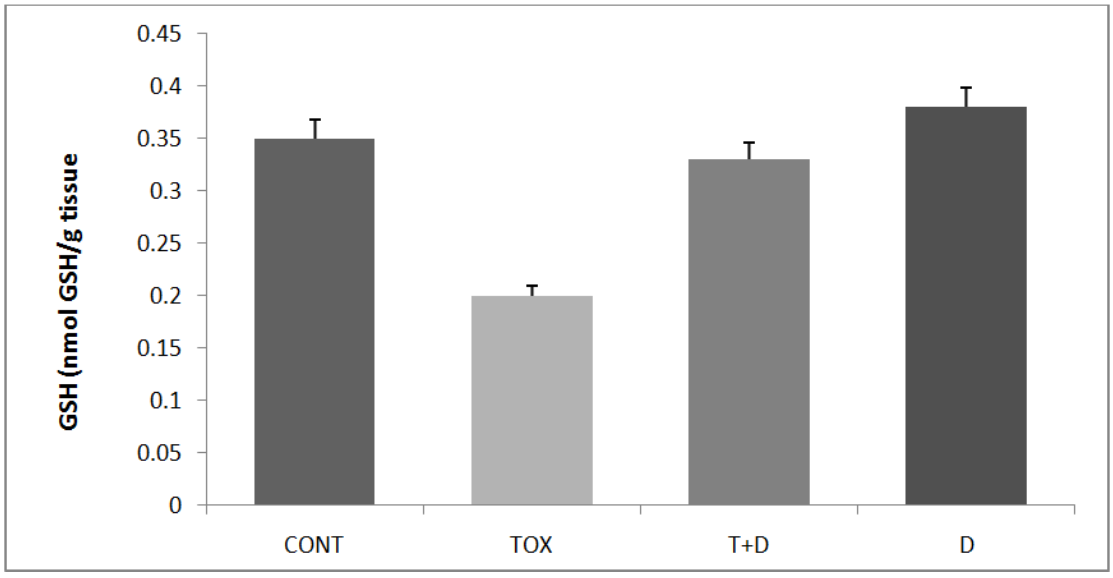

Figure. 1

CONT = Saline Only, TOX = CP Only, D + T = CP + BT, D = BT Only

Effect of BT pre-treatment on renal GSH induced by CP, the values represent mean±SEM. MDA content was significantly ($P \leq 0.05$) if compared with control group. BT= β-sitosterol, CP = Cisplatin.

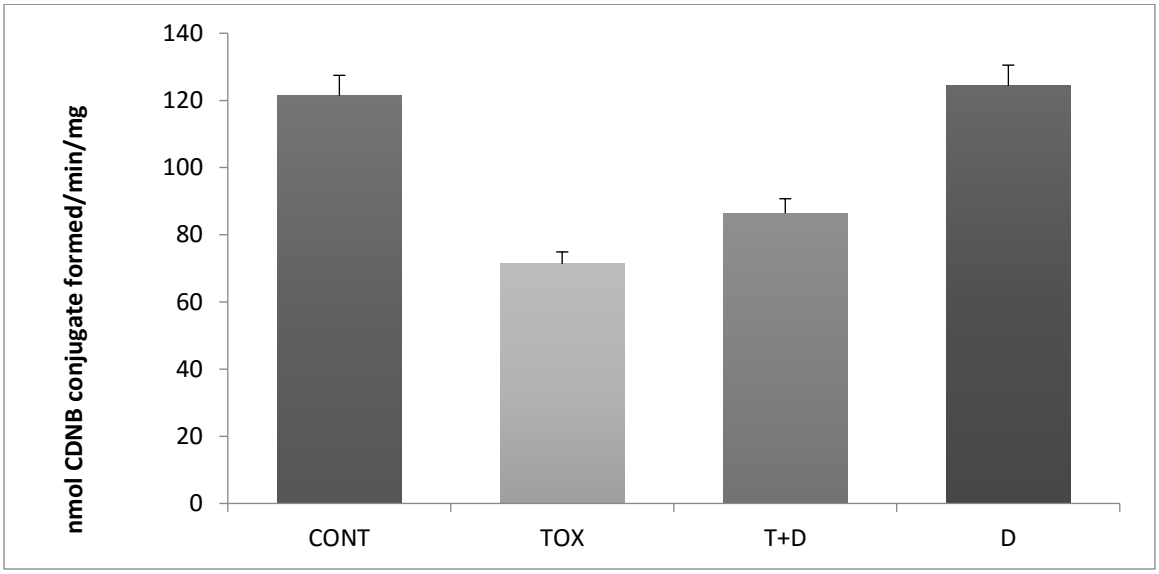

Figure 2.

CONT = Saline Only, TOX = CP Only, D + T = CP + BT, D = BT Only

Effect of BT pre-treatment on renal GST induced by CP. the values represent mean±SEM. MDA content was significantly ($p \leq 0.05$) if compared with control group. BT= β-sitosterol, CP = Cisplatin.

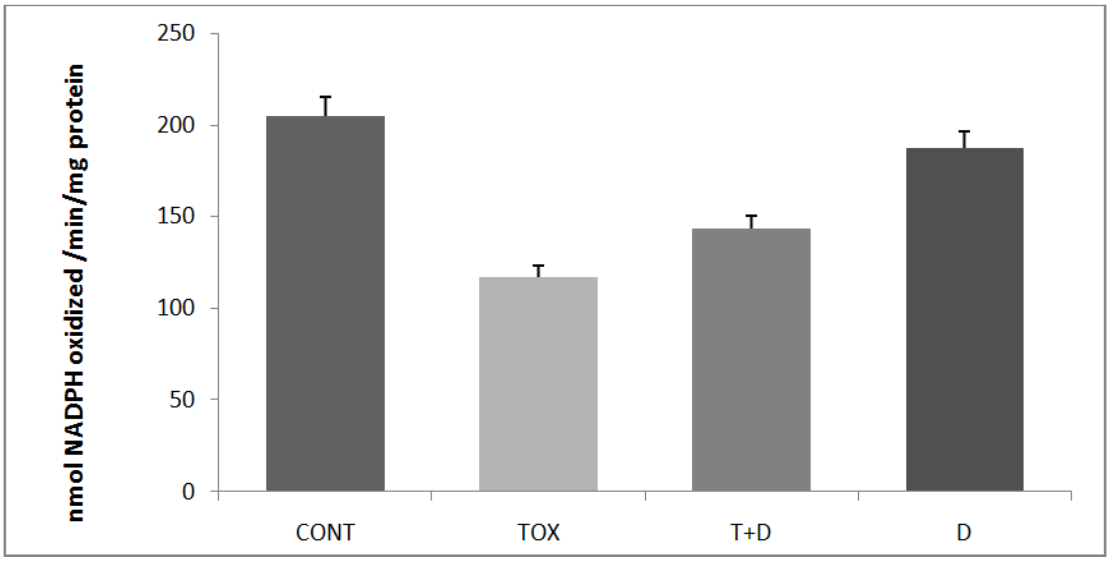

Figure 3.

CONT = Saline Only, TOX = CP Only, D + T = CP + BT, D = BT Only

Effect of BT pre-treatment on renal GR induced by CP. the values represent mean±SEM. MDA content was significant ($P \leq 0.05$) if compared with control group. BT= β-sitosterol, CP = Cisplatin.

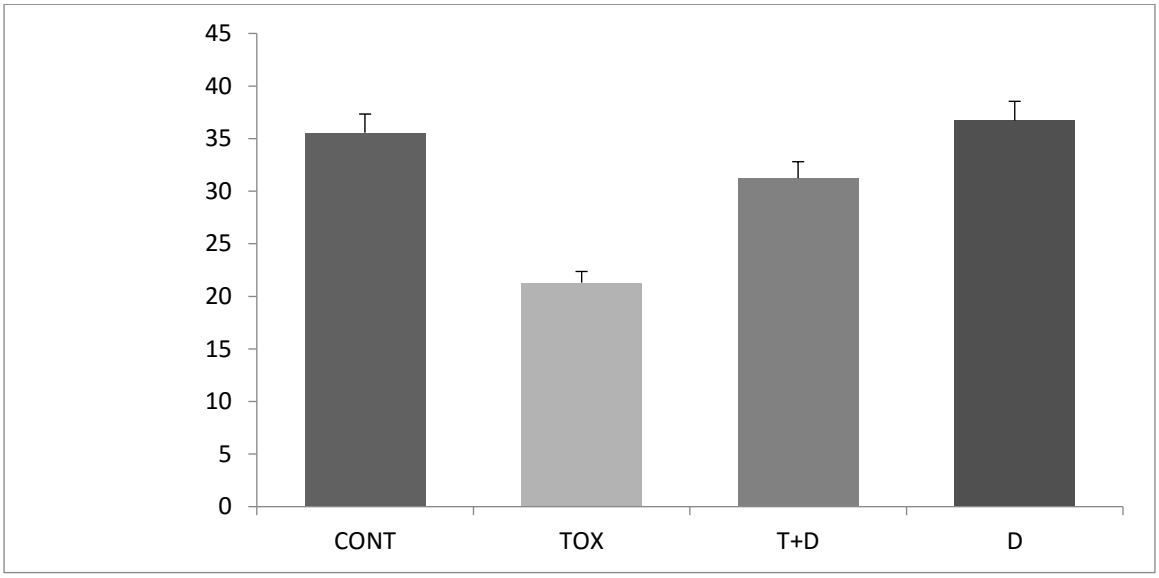

Figure 4.

CONT = Saline Only, TOX = CP Only, D + T = CP + BT, D = BT Only

Effect of BT pre-treatment on renal Catalase induced by CP. the values represent mean±SEM. MDA content was significant ($P \leq 0.05$) if compared with control group. BT= β-sitosterol, CP = Cisplatin.

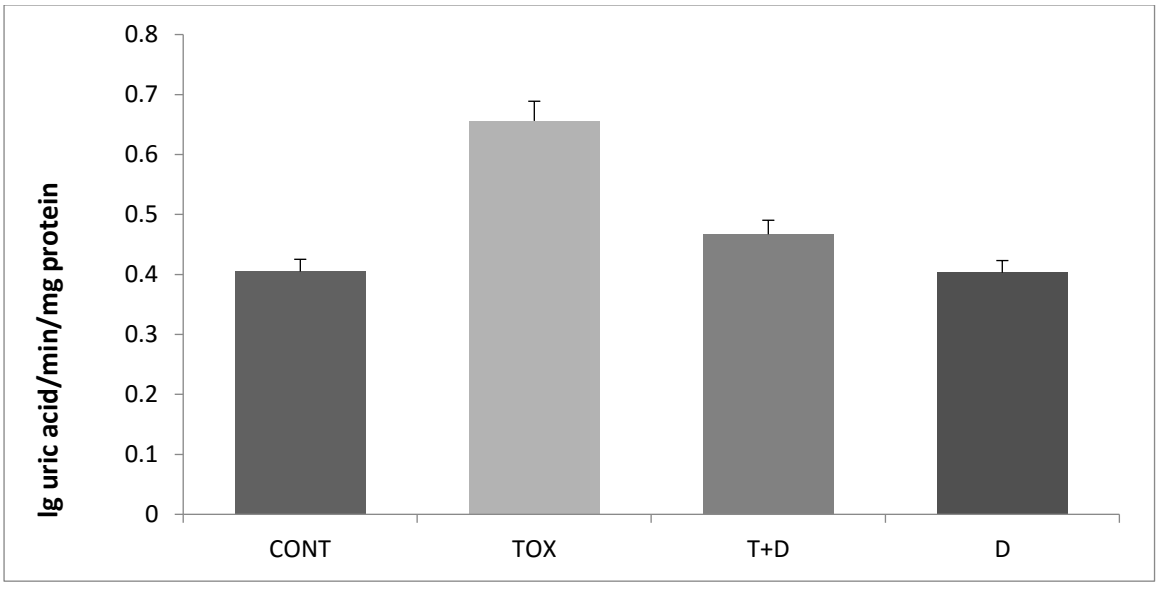

Figure 5

CONT = Saline Only, TOX = CP Only, D + T = CP + BT, D = BT Only

Effect of BT pre-treatment on renal Xanthine Oxidase induced by CP. the values represent mean ± SEM. MDA content was significant ($p \leq 0.05$) if compared with control group. BT= β-sitosterol, CP = Cisplatin.

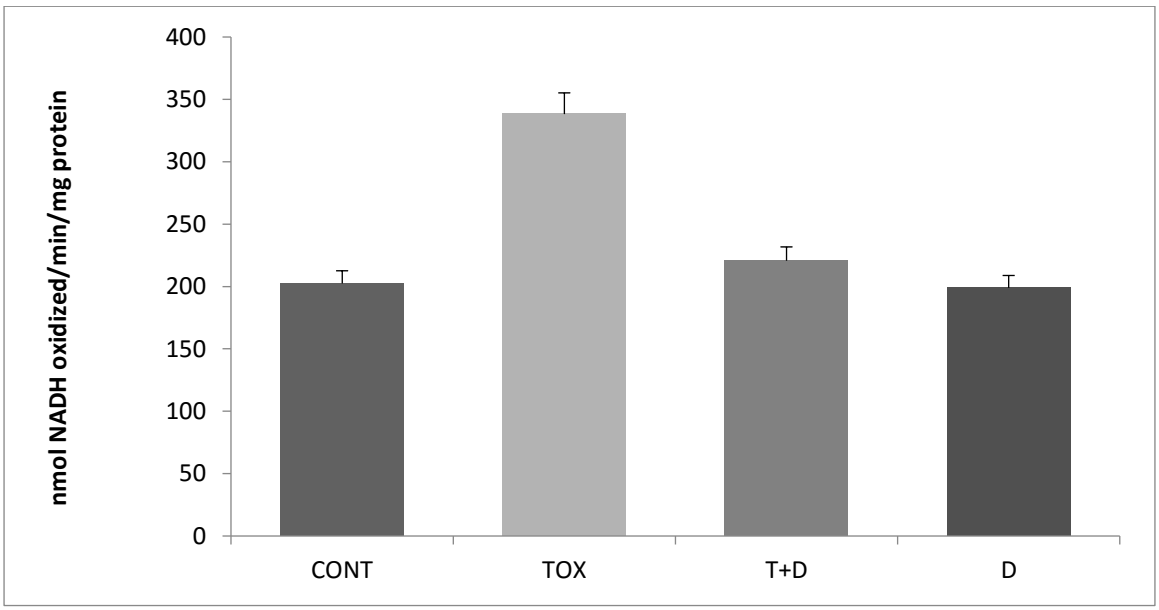

Figure 6.

CONT = Saline Only, TOX = CP Only, D + T = CP + BT, D = BT Only

Effect of BT pre-treatment on renal Lactate dehydrogenase induced by CP. the values represent mean±SEM. MDA content was significant ($p \leq 0.05$) if compared with control group. BT= β-sitosterol, CP = Cisplatin.

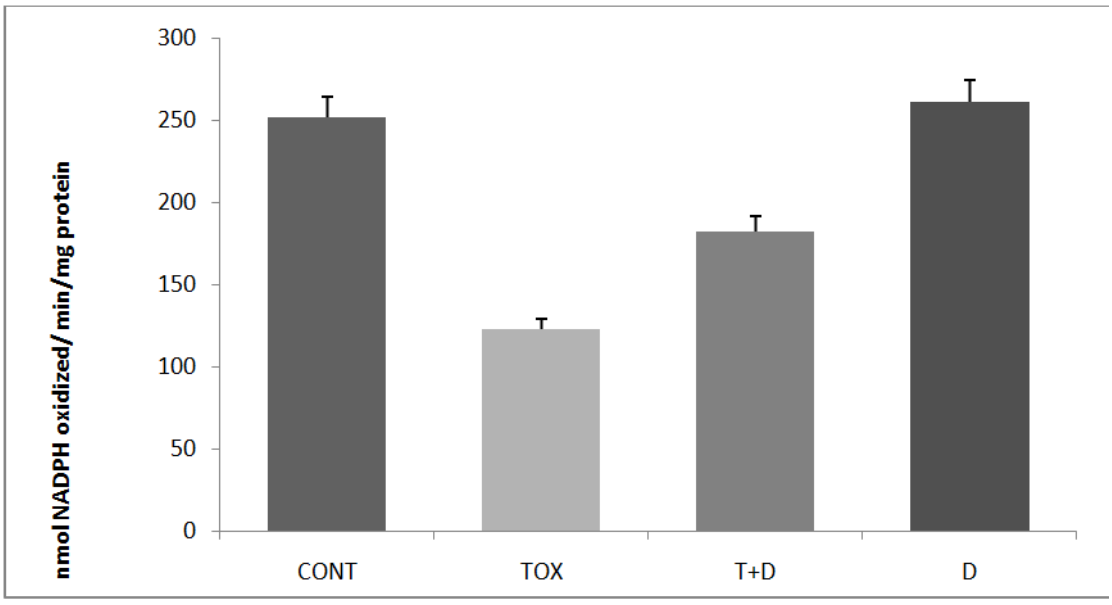

Figure 7.

CONT = Saline Only, TOX = CP Only, D + T = CP + BT, D = BT Only

Effect of BT pre-treatment on renal Quinone Reductase induced by CP. the values represent mean±SEM. MDA content was significant ($p \leq 0.05$) if compared with control group. BT= β-sitosterol, CP = Cisplatin.

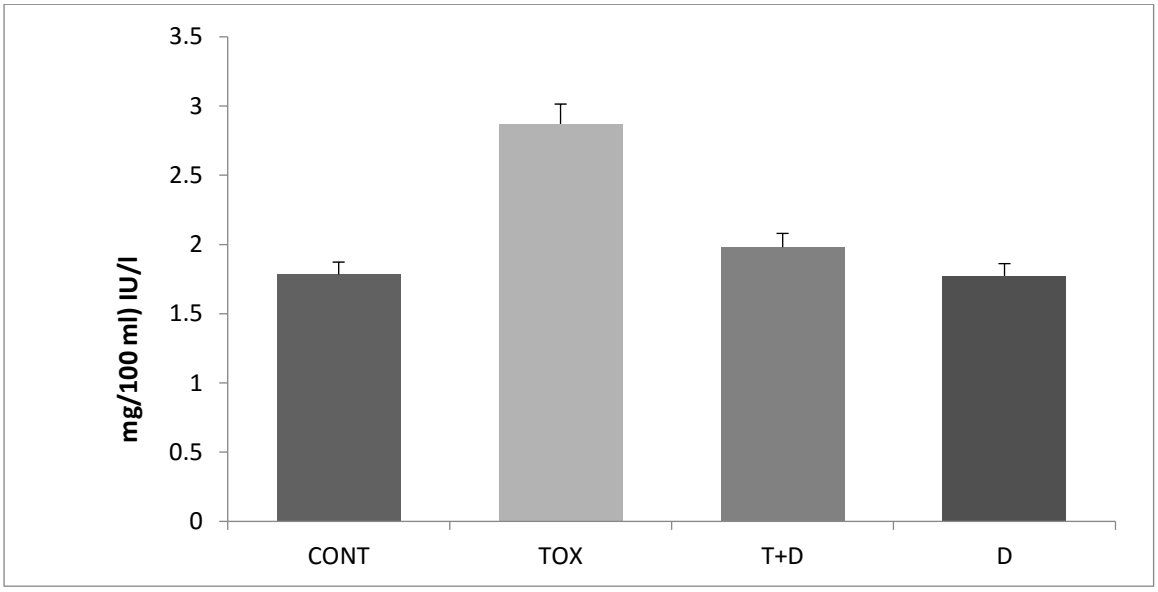

Figure 8.

CONT = Saline Only, TOX = CP Only, D + T = CP + BT, D = BT Only

Effect of BT pre-treatment on renal Creatinine induced by CP. the values represent mean±SEM. MDA content was significant ($p \leq 0.05$) if compared with control group. BT= β-sitosterol, CP = Cisplatin.

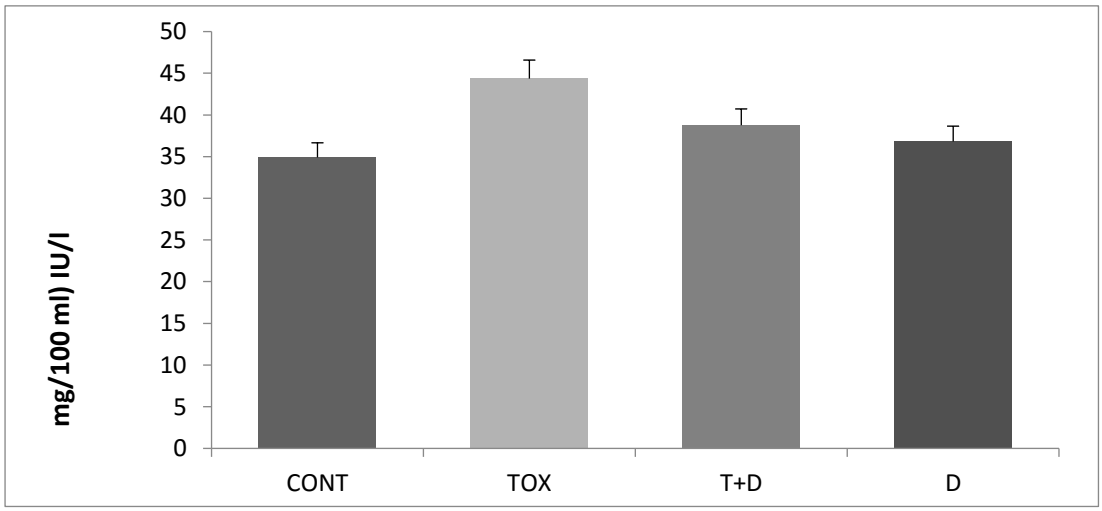

Figure 9.

CONT = Saline Only, TOX = CP Only, D + T = CP + BT, D = BT Only

Effect of BT pre-treatment on renal Blood Urea Nitrogen induced by CP. the values represent mean±SEM. MDA content was significant ($p \leq 0.05$) if compared with control group. BT= β-sitosterol, CP = Cisplatin.

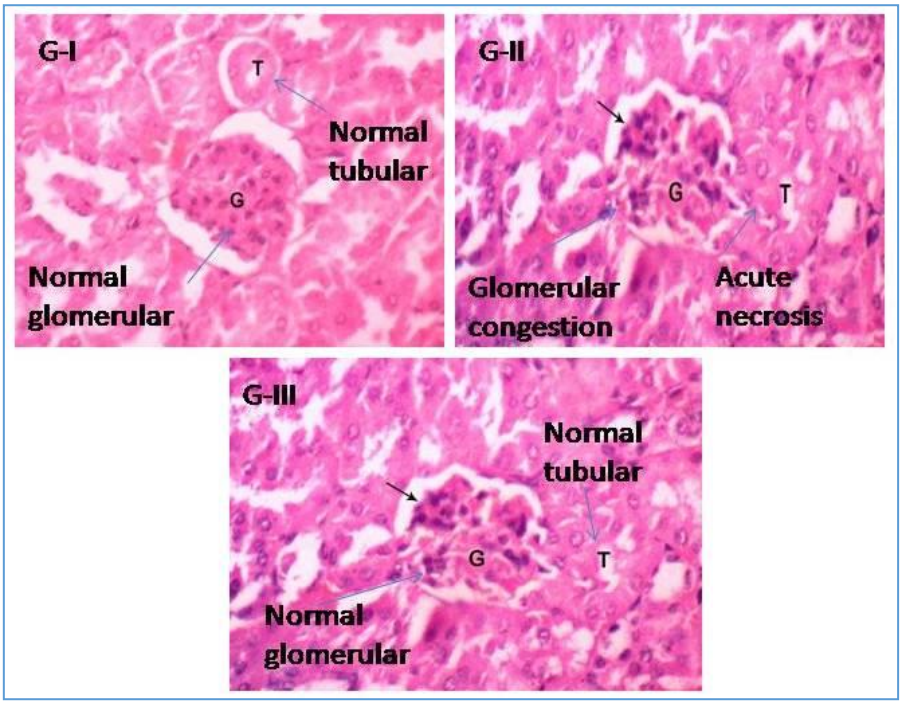

Figure 10.

Photomicrographs (magnification E 400x), the kidney tissue showed glomerular and tubular histology are normal and in both in cortical and medullary region in control group. Representatively, CP (7.5 mg/kg b. wt.) treated was found to cause severe interstitial edema, glomerular and peritubular necrosis (group II), as compared with control (group 1). The histological features demonstrated marked a significant a reduction in renal injury in group (3), if compared with (group 2). pre-treatment of BT (5 mg/kg b wit) was shown no any a significant change in group IV, as compared with control (group I).

Table 1 depicts the effect of β-sitosterol (BT) pre-treatment with cisplatin (CP) induced alterations in reduced glutathione (GSH) content and its redox cycle. Treatment with cisplatin result in the reduction of renal reduced glutathione, glutathione S-transferase and Glutathione reductase significantly ($p<0.002$), while β-sitosterol treated groups showed restoration of glutathione redox cycle enzymes and GSH levels. The effect of β-sitosterol (BT) on cisplatin (CP) results decrease activities of antioxidant enzymes in kidney, as the Table 2. Like catalase, xanthine oxidase and lactate dehydrogenase if compare with first group. Treatment with β-sitosterol (BT) at the lower dose of 5 mg/kg body weight caused recovery of the above enzymes significantly ($p<0.004$), as compared with the cisplatin treated group. Table 3 shows that β-sitosterol (BT) treatment enhances the activity of Quinone Reductase, Creatinine and BUN; susceptibility of renal microsomal membrane for iron-ascorbate induced lipid peroxidation and H_2O_2, as compared to controls. when treated by

Cisplatin (CP) results reduction in Quinone Reductase activity, Creatinine and BUN; and lipid peroxidation in renal microsomal significantly (P<0.001), whenever compare with cisplatin group. Examination of Histopathological of kidneys tissue in rats revealed glomerular and tubular histology are normal in cortical and medullary region in first group. CP (7.5 mg/kg b. wt.) cisplatin (CP) treated group was found to cause extremely severe interstitial edema, glomerular and peritubular necrosis as shown (Figure 4), the morphological showed widespread degeneration of swelling, necrosis and tubular congestion. In contrast, renal sections obtained from rats, pre-treated with β-sitosterol (BT) (5 mg/kg b wit), the histological features demonstrated marked a significant reduction in renal injury in group III as presented (Figure 4), β-sitosterol (BT) treated group IV (5 mg/kg b wit) was not showing any a significant change.

Discussion

Over the past five decades cisplatin (CP) being used as an antineoplastic agent via alkylating addiction with DNA [38]. It has limited myelosuppression, hepatotoxicity, nephrotoxicity and ototoxicity. cisplatin (CP) has ability to accumulate in mitochondria, cytosol, microsomes and nuclei, at the high dose. Nephrotoxicity is a predisposing factor to the development of kidney filter [39,40]. In our paper, the focus of attention on employed of biochemical parameters with histopathology finding was seen after cisplatin (CP) treatment in rodent models, which is much earlier finding of its effect of nephrotoxic [41,40]. The Kidney tissue damage by oxidative stress is closely associated with the pathogenesis of cisplatin induced acute nephrotoxicity. Previous studies indicate that oxidative stress that occurs due to several agents is related strongly with the histopathology changes [43,44]. the cell components effected by Reactive oxygen species (ROS), including lipids, proteins, and damage their integrity. In the cell, ROS was produced by system of the xanthine oxidase, mitochondria, NADPH oxidase and pathogenesis of cisplatin (CP) induced renal injury have close association with indication formation Reactive oxygen species [45]. The experimental results showed cisplatin (CP) treatment, causes inhibit the activity of antioxidant enzymes (glutathione-S-transferase, glutathione, reductase and catalase) in kidney rats. The results obtained by Afifi in [46] suggest that cisplatin (CP) treatment act to decrease of glutathione activities and reduction of antioxidative system in kidney tissue. In additon, GR and GST, were significantly restored to normal levels in levels in BT treated of CP group.

Furthermore, β-sitosterol (BT) treated to restore the decreased levels of QR and catalase. some early studies found cisplatin (CP) results nephrotoxicity by lipid peroxidation with a reducing cellular thiols content [47]. In this work has shown that, a clear realised raise level of LPO activity and accompany with histopathology changes like severe interstitial edema, glomerular and peritubular necrosis in the cisplatin (CP) treated group; Moreover, Previous research has demonstrated that LPO is noticeable reduce through treated with plant derived compounds [48]. This work has highlighted that, β-sitosterol (BT) pre-treated of cisplatin (CP) given rats significantly reduce XO and MDA activities. Complementary modification of antioxidant system was also noted. Serum kidney toxicity parameters were clearly observed, that reported in previous work [49]. In addition, GR and GST, were significantly normal levels in BT treated of cisplatin (CP) group. Furthermore, β-sitosterol (BT) treated to restore the decreased levels of QR and catalase, as earlier reports suggested that cisplatin (CP) induces nephrotoxicity by induced lipid peroxidation with reducing cellular thiols content [47]. In this study conduct to β-sitosterol (BT) on cisplatin (CP) treated group significantly decreased serum toxicity parameters with main histological finding which refer to enhanced recovery of kidney toxicity, therefore increasing an act for β-sitosterol (BT) in altering nephrotoxicity. β-sitosterol (BT) treated group have a significant reduced BUN, LDH and creatinine activates as comparative with cisplatin (CP) group; therefore, β-sitosterol (BT) modulation kidney toxicity.

In conclusion, β-sitosterol (BT) has attenuates the nephrotoxicity of cisplatin (CP) in rats, and might be clinically useful, further research will be required to prove molecular studies in this regard before it can be taken for clinical trials. In the present study, β-sitosterol (BT) showed protective effects against cisplatin (CP) induced nephrotoxicity by inhibiting oxidative stress, maintaining balance of antioxidant (enzymatic and nonenzymatic) in rodents, the nephroprotective capacity of β-sitosterol (BT) is possibly because of free radical scavenging and antioxidant property.

Conflict of interest

The authors declare that there are no conflicts of interest.

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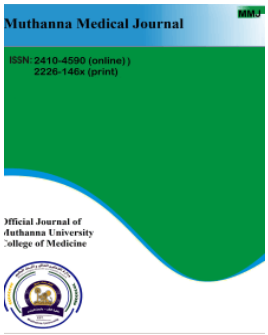

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