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ORIGINAL ARTICLE

Raloxifene Inhibits NF-kB Pathway and Potentiates Anti-Tumour Activity of Cisplatin with Simultaneous Reduction in its Nephrotoxictiy

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Abstract Cisplatin induced nephrotoxicity is the chief obstacle in the use of cisplatin as chemotherapeutic agent. However, it remains as most widely employed anticancer agent to treat various solid tumours like head-neck, testicular, ovarian and mammary gland cancer. Raloxifene is claimed to be potent anti-inflammatory as well as anti-cancer agent. The present study was carried out to explore the effect of pre-treatment of raloxifene on cisplatin induced nephrotoxicity and its anti-tumour activity in 7, 12 dimethyl benz [a] anthracene induced mammary tumour in animal model. Renal damage was accessed by measuring serum level of creatinine, blood urea nitrogen and albumin whereas systemic inflammation was accessed by measuring level of pro-inflammatory cytokines like tumour necrosis factor alpha (TNF-α), interleukin 6 (IL-6), interleukin 10 (IL-10) and nuclear factor kappa B (NFκB). Moreover, assessment of tumour reduction was done by measuring tumour volume and percentage tumour reduction. A single dose of cisplatin (7.5 mg/kg) resulted in significant increase in serum creatinine, blood urea nitrogen, NF-kB, TNF-α and IL-6 levels along with decrease in albumin and IL-10 levels. However, there were no significant changes in raloxifene (8 mg/kg) treated group. Pre-treatment of raloxifene (8 mg/kg) caused marked decrease in serum creatinine, blood urea nitrogen, TNF-α and IL-6 levels whereas increase in albumin and IL-10 levels. However, pre-treatment of raloxifene showed maximum tumour reduction as compared to cisplatin and raloxifene treated groups. The present study demonstrates that raloxifene potentiates anti-tumour activity of cisplatin with simultaneous reduction in its nephrotoxicity, and this effect is attributed to its direct anti-inflammatory activity.

Keywords Cisplatin · Raloxifene · Nephrotoxicity · Inflammation · Pro-inflammatory cytokines

Introduction

Cisplatin, aka cis-DDP (cis-diamminedichloro-platinum(II)) is one of the most widely used antitumour agent for the treatment of solid tumours like head and neck, ovarian, testicular and mammary tumours [1, 2]. Cisplatin being the first big chemotherapy drug to treat wide range of cancers, Kelland et al. in 2007 regarded it as "penicillin of cancer" [3]. Hitherto, the mechanism of action of cisplatin is not fully understood, but it has been reported that it interferes with repair mechanism of cancer cells by binding irreversibly to DNA. However, major drawback of cisplatin's chemotherapy is its dose dependant nephrotoxicity [4, 5]. This is foremost side effect ensuing 28–36 % of patients nephrotoxic on single cisplatin injection [6]. How does cisplatin cause nephrotoxicity is still a mystery but most of the reports says it damages renal cells, causing tubular toxicity mediated by apoptosis, necrosis and inflammation [7]. In contrast to its renal toxicity, cisplatin remains widely prescribed antineoplastic drug against sarcomas [8].

Cisplatin's dose intensity is of vital concern in its therapy as it possess dose dependent efficacy. However, it has been reported that cisplatin in high doses leads to cumulative renal

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and nerve damage. So, there is a need to determine a priori cisplatin doses and schedules that will provide therapeutic benefit and cause minimum toxicity [9]. Recent studies showed that inflammation and inflammatory mediators like interleukins, leukocytes, adhesion molecules, chemokines, and cytokines are strongly instrumental in cisplatin induced nephrotoxicity [10]. Moreover, the presence of activated pro-inflammatory cytokines, chemokines, interleukins and adhesion molecules during cisplatin therapy clearly shows the role of inflammation in cisplatin induced renal injury [11, 12]. The major role of TNF-α in cisplatin induced nephrotoxicity through activation of NFκB pathway in the kidney following cisplatin injection has also been recently reported [13]. Therefore, cisplatin induced renal damage can be effectively appeased by concurrently administering drugs that can inhibit the NFκB pathway and selectively prevent TNF-α synthesis or block its activity [14].

Raloxifene is selective estrogen receptor modulator used in post-menopausal women osteoporosis and in breast cancer therapy as well [15–17]. Olivier et al. have shown raloxifene as inhibitor of nuclear factor-κB (NFκB) in myeloma cells by removing p65 subunit from its binding sites through estrogen receptor α interaction with p65 subunit [18, 19]. Several studies have reported key role of NFκB in growth as well as survival of tumour cells and it is an important target for a number of diseases [20, 21]. NFκB plays pivotal roles in inflammatory responses and immunological reactions whose activation results in enhanced secretion of TNF-α and various interleukins such as IL-6, IL-1β and reduced secretion of IL-10 [20, 22–25]. Based on above facts it was hypothesized that pre-treatment of raloxifene could have beneficial effect in cisplatin induced nephrotoxicity, because raloxifene has been recently demonstrated to inhibit NFκB, which intern leads to reduced level of TNF-α and interleukins, which are present in the cells of renal parenchyma and predominantly mediates anti-inflammatory effect (Fig. 1).

Methods

Materials

Cisplatin, raloxifene and 7, 12-dimethyl Benz [a] anthracene were bought from Sigma (St. Louis, MO, USA). Blood urea nitrogen (BUN), creatinine and albumin kits were purchased from Idexx vetlab (Mumbai, India). Cisplatin solution was prepared in normal saline (0.9 % NaCl) and raloxifene dissolved in olive oil (100 μl). All the solutions were prepared freshly before the experiment.

Animals

The guidelines of committee for the purpose of control and supervision of experiments on animals (CPCSEA Registration No. 351; 3/1/2001), Government of India were followed and prior consent was sought from the institutional animal ethics committee (IAEC) (Approval no. MC/32/2013/28) for conducting the work. The female Wistar rats (200–2400 g; 7–8 weeks old) were procured from the central animal facility of the institution (Gauhati Medical College, Guwahati). They were kept under standard environmental conditions and supplied with normal pellet diet and water ad libitum. Bearing in mind the animal ethical issues, all animals were maintained under best sanitary conditions and the animals were inspected regularly for any signs of pain, discomfort or distress. A total of 42 adult female Wistar rats were used in the study. They were housed separately in polypropylene cages. The animals were kept under the experimental housing and normal feeding conditions for 7 days before the test. The animal room was maintained at 22 ± 2 °C, 60 ± 15 % relative humidity, and 12:12 h light–dark cycle.

Tumour Induction

8 weeks old female Wistar rats weighing 200–2400 g were gavaged with 65 mg 7, 12-dimethylbenz [a]anthracene (DMBA)/kg body weight (Fig. 2). This dose is sufficient to cause 100 % tumour induction in the control group over the course of the study as described by Whitsett T et al. [26]. The DMBA was dissolved in olive oil at a stock solution of 30 mg/ml. The DMBA took 14 weeks to induce mammary tumour in female Wistar rats. Animals were sacrificed when the tumour diameter reached 3 cm, animals became moribund or after the completion of experiment.

Study Design and Treatment

Initially rats were divided in two equal group's namely, normal control (Group I) and DMBA treated group which received normal saline and 65 mg/kg DMBA respectively. After 12 weeks when mammary tumour was induced the DMBA treated group was further divided in four different groups on the basis of tumour volume. DMBA treated rats received vehicle (Group II). The mammary tumour induced rats were treated with raloxifene (8 mg/kg) (Group III) dissolved in 100 μl olive oil through oral gavage for 5 days. The mammary tumour induced rats were treated with cisplatin (7.5 mg/kg) dissolved in normal saline by intra-peritoneal route (Group IV). The mammary tumour induced rats were pre-treated with raloxifene (8 mg/kg) (Group V) dissolved in 100 μl olive oil for 5 days through oral gavage and then on fifth day single dose of cisplatin (7.5 mg/kg) dissolved in normal saline (0.9 % *w*/*v*) by intra-peritoneal route (Fig. 2). Blood was

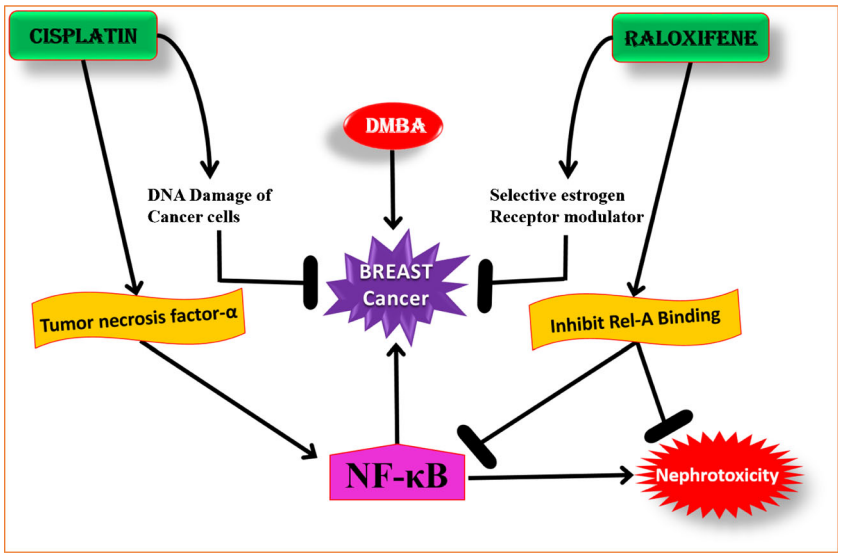

Fig. 1 Pictorial representation of mechanism of raloxifene and cisplatin in prevention of breast cancer and cisplatin induced nephrotoxicity. DMBA- 7, 12-dimethyl benz {a} anthracene and NFκb – Nuclear factor kappa B

collected from tail vein under light ether anaesthesia. Animals were sacrificed, a midline incision was made and both the kidneys were removed; the left kidney was deeply frozen till further enzymatic analysis, whereas the right kidney was stored in 10 % formalin for the histological studies.

Estimation of Serum Albumin, Blood Urea Nitrogen and Creatinine

Blood samples were collected and immediately centrifuged at 8000 rpm for 10 min at 4^0c. The serum was separated and stored at −80° C until assayed. It was then used for the estimation of albumin, blood urea nitrogen (BUN) and creatinine using Idexx vet analyser.

Measurement of NFκB, TNF-α, IL-6 and IL-10 Levels

The level of ***NFκB***, TNF-α, IL-6 and IL-10 in serum was determined by using enzyme linked immunosorbent assay (ELISA) kits (Sigma Aldrich, India), according to the manufacturer's instructions. In all the cases, a standard curve was constructed from standards provided by the manufacturer.

Measurement of Tumour Volume

The measurements were done for visible tumours; two diameters that is shortest and longest diameter of the tumours were measured. The volume of the tumour was calculated as: $\Pi/6.(a)^2(b)$, where a is the smallest and b is the longest length of the tumour [27].

Histopathology of Mammary Tumour and Kidney

Histopathology of mammary tumour and kidney was done as described previously (Tikoo et al., 2009a, 2007, 2009b, 2008). Briefly, rats were anesthetized under light ether anaesthesia; after surgery, circulating blood was removed by cardiac perfusion with 0.1 MPBS (pH 7.4; 20–50 ml). After clearing

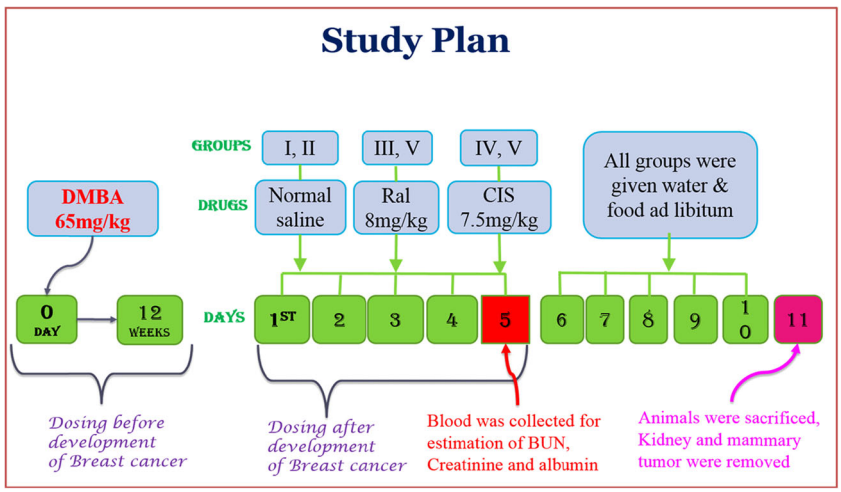

Fig. 2 Study plan showing dosing before and after development of breast cancer

circulating blood and adhering tissues, 4 % paraformaldehyde in 0.1 M phosphate buffer (pH 7.4) was perfused for another 5 min (100–200 ml of fixative) to fix the tissues. The mammary tumour and kidneys were removed from the animal, decapsulated, sliced transversely, and paraffin embedded for light microscopic evaluation. Histopathological changes in these tissues were assessed in at least 25 randomly selected tissue sections from each group studied. Sections were stained with Mayer's haematoxylin and eosin to examine the changes in cell structure. The stained sections were observed under microscope (Leica DM 750) at magnification of 40×.

Statistical Analysis

Experimental values are expressed as mean ± SEM. Comparison of mean values between various groups was performed by one way analysis of variance (one way ANOVA) followed by multiple comparisons by Tukey's test. P value <0.05 is considered to be significant.

Results

Effect of Raloxifene Pre-treatment on Cisplatin Induced Changes Levels of Creatinine, Blood Urea Nitrogen, Albumin, Body Weight and Kidney Weight

Effects of administration of raloxifene (8 mg/kg), cisplatin (7.5 mg/kg) and pre-treatment with raloxifene (8 mg/kg) + cisplatin (7.5 mg/kg) on creatinine, BUN and albumin in rats are shown in Fig. 3. Cisplatin treatment group showed substantial increase in the level of creatinine, when compared with breast cancer control group. There was no significant increase in creatinine in raloxifene control group. However, pre-treatment of raloxifene resulted in significant decrease in serum creatinine level when compared with cisplatin treated group. Moreover, Cisplatin treated group showed substantial increase in level of blood urea nitrogen, as compared to breast cancer control group. There was no significant increase in BUN in raloxifene treated group. However, pre-treatment of raloxifene resulted in significant decrease in serum blood urea nitrogen level when compared with cisplatin treatment group. In contrast to the level of creatinine and BUN, there was significant decrease in albumin level in cisplatin treatment group whereas pre-treatment of raloxifene showed significant increase in albumin level when compared with breast cancer control group.

Cisplatin treatment group showed significant decline in body weight of animals when compared with normal control group. However, pre-treatment of raloxifene showed significant increase in body weight compared with cisplatin control. Furthermore, cisplatin treated group showed significant gain in kidney weight when compared with breast cancer control as well as normal control. Whereas, pre-treatment with raloxifene followed by cisplatin administration have prevented the kidney weight gain compared with cisplatin treated rats.

Effect of Raloxifene and Cisplatin on NFκB p65 Subunit

Effects of administration of raloxifene (8 mg/kg), cisplatin (7.5 mg/kg) and pre-treatment with raloxifene (8 mg/kg) + cisplatin (7.5 mg/kg) on level of NFκβ p65 subunit in rats is shown in Fig. 4. NFκβ p65 subunit levels were significantly elevated in the cisplatin treated group when compared with breast cancer control group. There was no significant decrease in raloxifene control group. However, pre-treatment of raloxifene resulted in significant decrease in NFκβ p65 subunit level when compared with cisplatin treatment group.

Effect of Raloxifene and Cisplatin on TNF-α, IL-6 and IL-10 Levels

According to various reports, it has been suggested that tumour necrosis factor alpha and interleukins plays a crucial role in cisplatin induced nephrotoxicity. Hence, curbing the secretion of TNF-α amends nephrotoxicity. Cisplatin showed significant increase in the level of TNF-α when compared with normal control group. Conversely, raloxifene pre-treatment significantly reduced TNF-α level in cisplatin treated group confirming that nephroprotection can be achieved by TNF-α inhibition (Fig.4). Moreover, cisplatin control group showed significant increase in IL-6 level when compared with normal control group. However, there was no significant change in IL-6 level in raloxifene control group. Raloxifene pre-treatment significantly reduced IL-6 level in cisplatin treated group when compared with cisplatin control group. However, cisplatin control group showed significant decrease in IL-10 level when compared with normal control group. There was no significant change in IL-10 level in raloxifene control group. Raloxifene pre-treatment significantly increased IL-10 level in cisplatin treated group when compared with cisplatin control group.

Effect of Raloxifene and Cisplatin on Tumour Volume and % Tumour Inhibition

Effects of administration of raloxifene (8 mg/kg), cisplatin (7.5 mg/kg) and pre-treatment with raloxifene (8 mg/kg) + cisplatin (7.5 mg/kg) on tumour volume in rats is shown in Fig. 5 Breast cancer control group showed substantial increase in tumour volume when

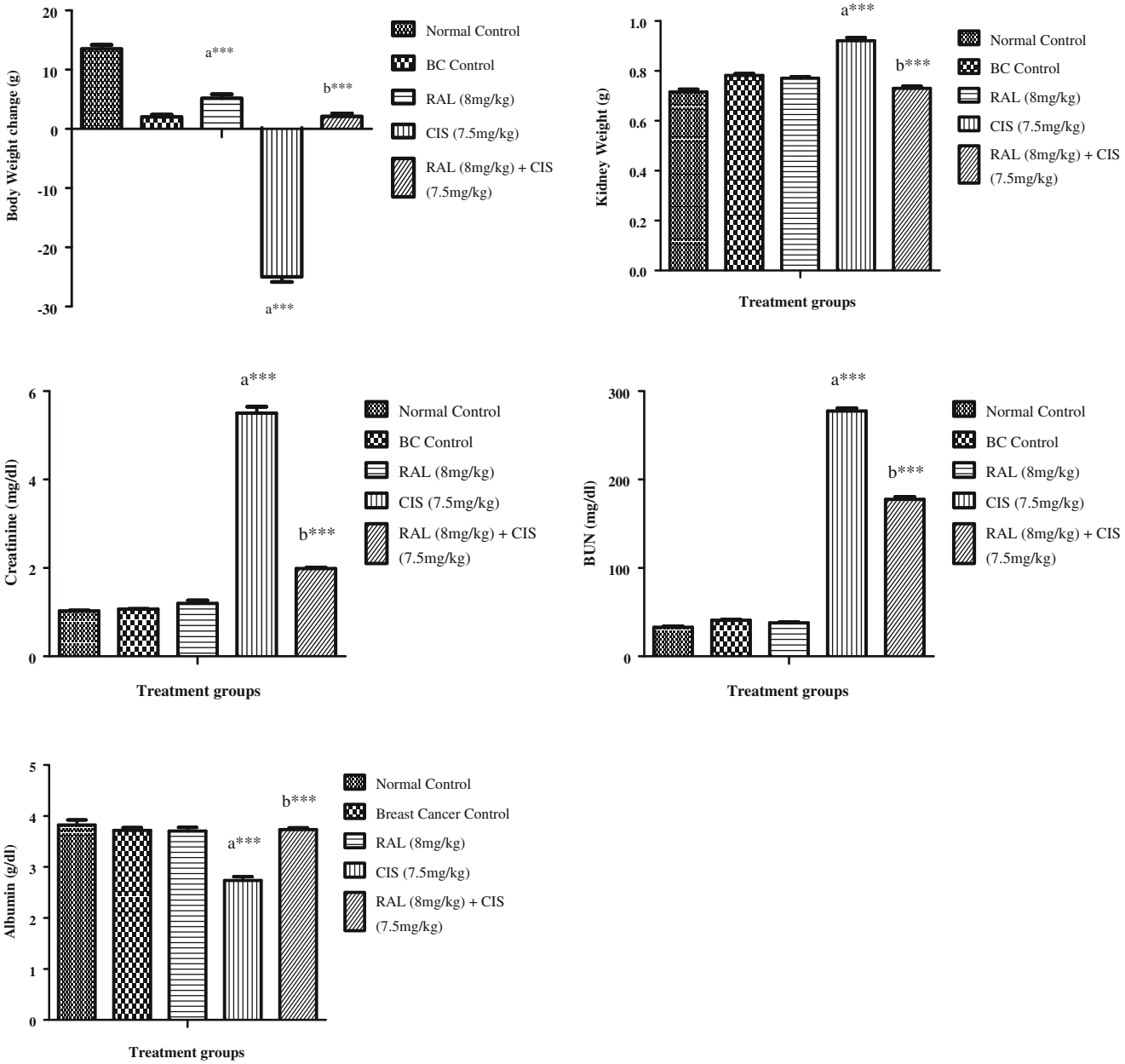

Fig. 3 Effect of raloxifene and cisplatin on body weight, kidney weight, creatinine, BUN and albumin in DMBA induced breast cancer. Effect of pretreatment on raloxifene followed by cisplatin on changes in Body weight, kidney weight, creatinine, BUN and albumin level in DMBA induced breast cancer in female Wistar rats. BC is breast cancer, RAL is raloxifene, CIS is cisplatinand PT is pretreatment. All the values were represented as Mean ± S.E.M. (n = 4), Statistical significance was determined by one-way ANOVA followed by Tukey's test. Values are statistically significant at $p < 0.05$. a Vs BC Control & b Vs Cisplatin

compared with treatment groups. However, pre-treatment of raloxifene resulted in significant decrease in tumour volume when compared raloxifene treated and cisplatin treatment group (Fig. 5).

There was significant tumour progression in breast cancer control rats when compared with raloxifene (8 mg/kg), cisplatin (7.5 mg/kg) and pre-treatment with raloxifene (8 mg/kg) + cisplatin (7.5 mg/kg) groups. In drug treated rats, tumour did not disappear totally, but a significant regression was found when compared with untreated rats. Raloxifene alone treated rats showed 25 % reduction on the 3rd day, 40 % reduction on 6th day and 58 % reduction on 9th day in the tumour size when compared with untreated animals. Again cisplatin treated group showed 20 % reduction on 3rd day, 34 % reduction on 6th day and 54 % reduction on 9th day when compared to untreated rats. In case of combined treatment groups there was 43 % reduction on 3rd day, 56 % reduction on 6th day and 76 % reduction on 9th day when compared with breast cancer control rats. Overall, the combined treatment

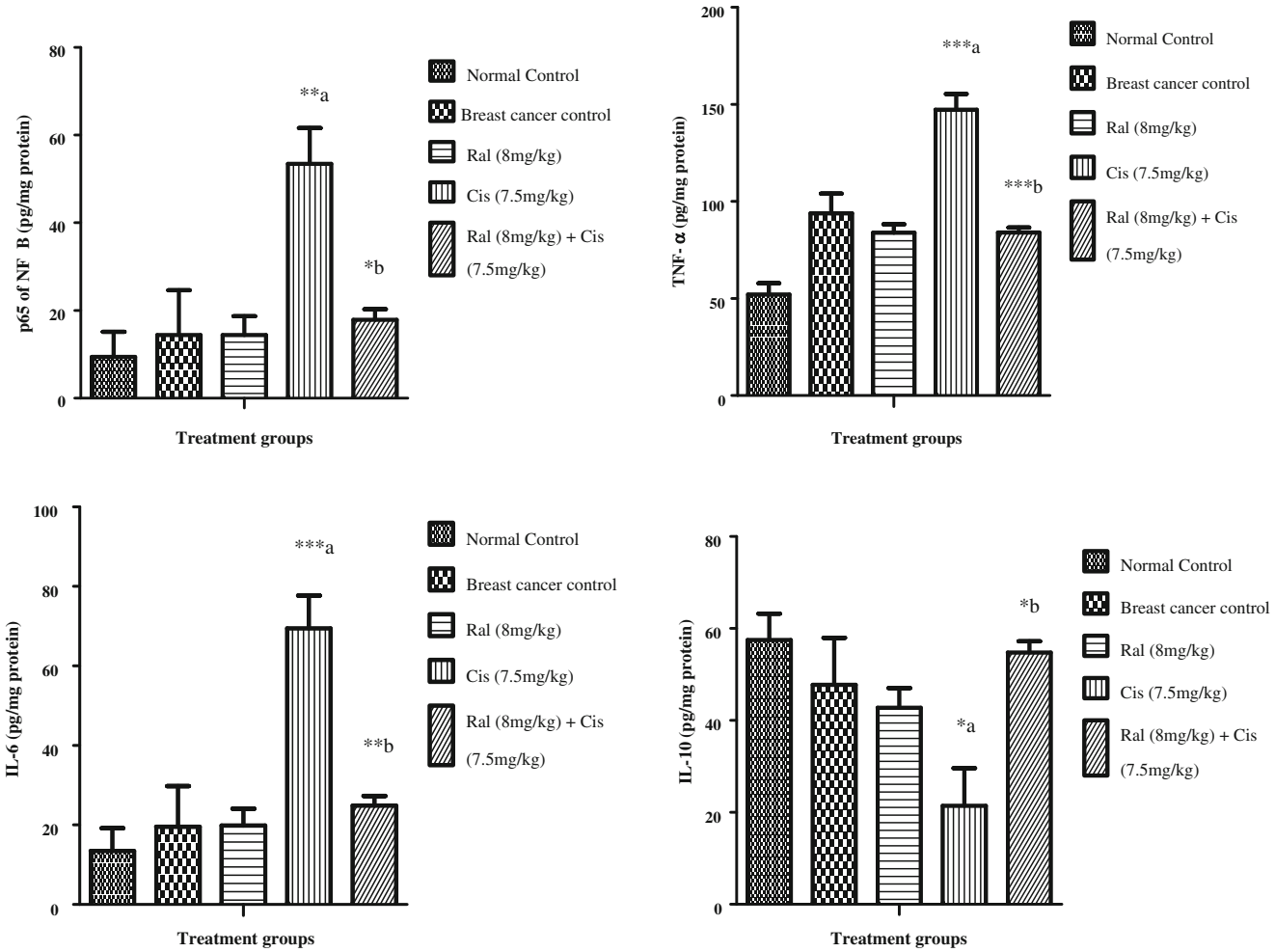

Fig. 4 Effect of raloxifene and cisplatin on TNF-α, IL-6, IL-10 and NF-κB p65 in DMBA induced breast cancer. Effect of raloxifene pretreatment on levels of TNF-α, IL-6, IL-10 and NF-κB p65 subunit followed by cisplatin administration in rats. Values are expressed as mean ± SEM for groups of four rats in each. Statistical significance was determined by one-way ANOVA followed by Tukey's test. Values are statistically significant at $p < 0.05$. a Vs Cancer Control & b Vs Cisplatin

group was more effective when compared with raloxifene and cisplatin treated groups.

Effect of Raloxifene and Cisplatin on Mammary Tumour Histology in DMBA Induced Breast Cancer

Breast cancer control group displays normal neoplasm histology (Fig.6, I). Raloxifene treated group showed, a low grade of differentiation which was demonstrated by giant cells (Fig.6, II). Decreased cell density and higher level of fibrosis was observed in cisplatin treated group (Fig.6, III). In the group, pretreated with raloxifene followed by cisplatin, the animals showed glandular structure as indicator for functional differentiation (Fig.6, IV). The presence of glandular structure in the histopathology of mammary tumour is an index of anticancer activity and our raloxifene pre-treatment showed glandular structures which were a clear cut indication of anticancer activity and it was maximum in this group because glandular structures were found only in combination group. This result was also supported by the tumour volume and percentage tumour inhibition parameters, i.e. on 9th day of raloxifene pre-treatment had shown maximum reduction in tumour volume and maximum percentage tumour inhibition when compared with all other groups like, breast cancer control, raloxifene control and cisplatin control (Fig. 5).

Effect of Raloxifene and Cisplatin Treatment on Changes in Renal Histology in Rats

Normal control rats showed intact renal tubules and glomeruli, in addition, uniform tubules with single layer of epithelium lining was observed in renal cortex of control rats (Fig. 7, I). Cisplatin treated rats showed increased tubular space, vacuolation and desquamation of epithelial cells in renal tubules (Fig. 7, III). However, pre-treatment with raloxifene dramatically improved the

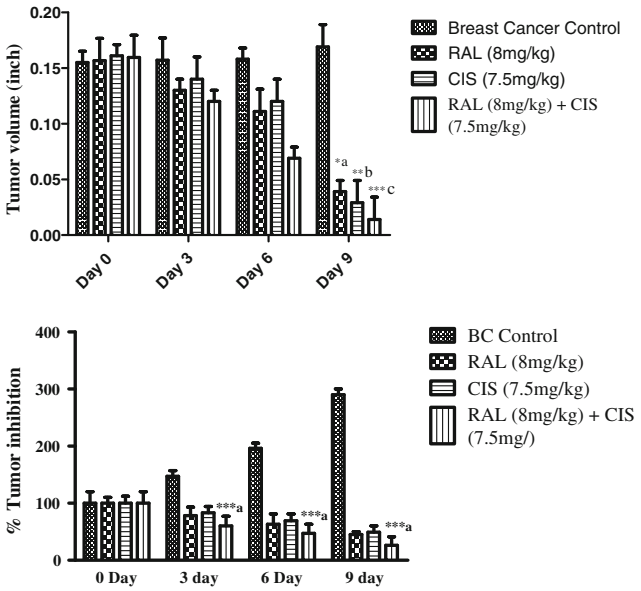

Fig. 5 Effect of raloxifene and cisplatin on tumour volume and % tumor inhibition in DMBA induced breast cancer. Effect of raloxifene pretreatment and cisplatin on tumour volume and % tumor inhibition in DMBA induced breast cancer in female Wistar rats. All values are expressed as mean ± SEM ($n = 4$). Where BC is breast cancer, RAL is raloxifene, CIS is cisplatin and PT is pretreatment. Tumour volume measured at 0 day, 3rd day, 6th day and 9th day. Values are statistically significant at $p < 0.05$. a Vs Raloxifene 0th day, b Vs Cisplatin 0th day and c Vs Raloxifene + Cisplatin 0th day

cisplatin nephrotoxicity showing minimum tubular damage in this group (Fig. 7, II). Raloxifene treatment alone had no effect on renal histology (Fig. 7, IV). This supports our data of biochemical protection observed in cisplatin induced nephrotoxicity.

Discussion

Regardless of its prominent nephrotoxicity, cisplatin remains extensively used drug to treat various solid tumours involving like mammary, testicular, ovarian, head and neck tumours. Hitherto, the exact mechanism of cisplatins nephrotoxicity is unknown. It is noted that cisplatin through mitogen activated protein kinase (p38) acts on tumour necrosis factor receptor (TNFR) 1 and tumour necrosis factor receptor (TNFR) 2 ensuing apoptosis and inflammation respectively leading to tissue damage [28]. TNFR 2 causes inflammation through release of cytokines and chemokines that causes tissue damage and this finally leads to acute kidney injury [12].

Single cisplatin injection begets toxicity to kidney tubule mainly in proximal convoluted tubules and some part of distal convoluted tubules, as substantiated by

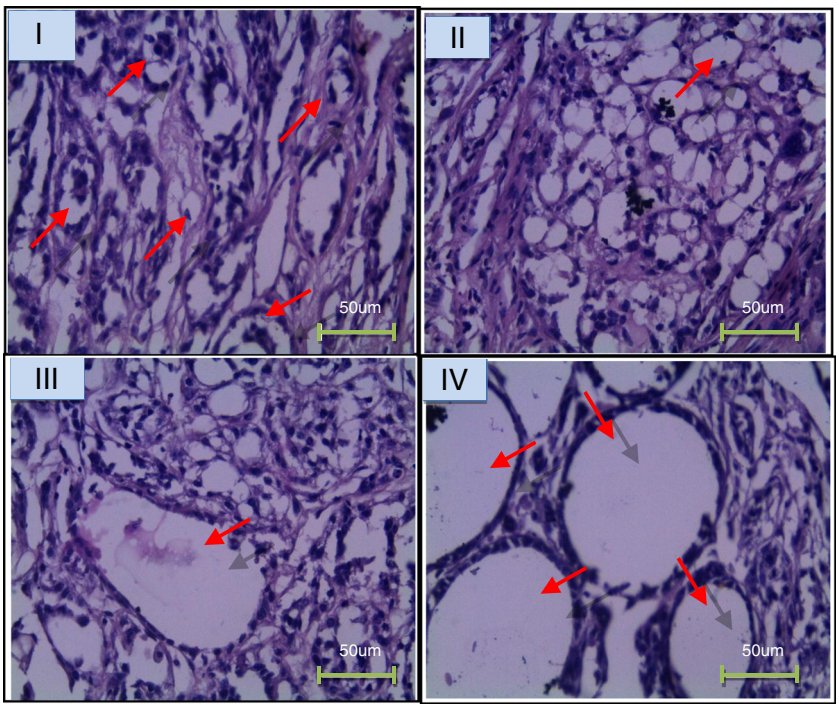

Fig. 6 Effect of raloxifene and cisplatin on mammary tumour histology in DMBA induced breast cancer. Histopathological effects of raloxifene and cisplatin on mammary tumour in rat. (I) Breast cancer control group. (II) Mammary tumour after treatment with raloxifene: The decreased cell density and higher level of fibrosis as sign of a therapeutic effect. (III) Cisplatin treated mammary tumour: pronounced cell pleomorphism and a low grade of differentiation are demonstrated by multinucleated giant cells. (IV) Pretreatment of raloxifene followed by cisplatin showed the glandular structure which is an indicator of functional differentiation and hence anticancer activity. Sections were stained with Mayer's haematoxylin counterstained with eosin and observed under magnification of 40X

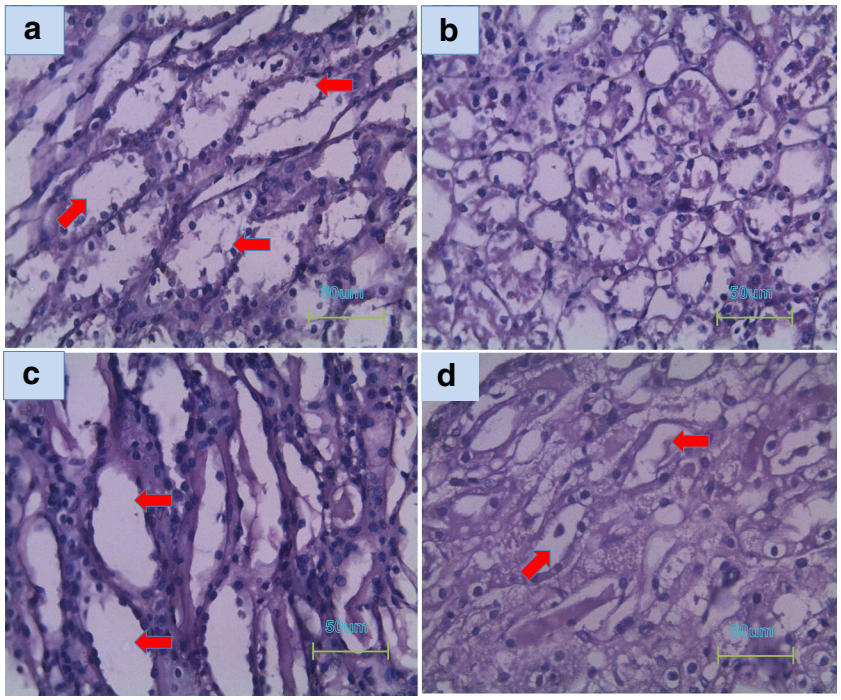

Fig. 7 Changes in renal histopathology in raloxifene and cisplatin treated groups. Histopathological effects of raloxifene and cisplatin on kidney in female Wistar rats. A transverse section of **a** Normal control group. **b** Kidney after treatment with raloxifene **c** Cisplatin treated kidney **d** Pretreatment of raloxifene followed by cisplatin. Sections were stained with Mayer's haematoxylin counterstained with eosin and observed under magnification of 40×

decreased creatinine and urea clearance [7, 10]. In present study we provide evidence that raloxifene pre-treatment significantly improved creatinine and urea clearance with increase in albumin level. We also provide evidence that raloxifene pre-treatment significantly decreased the level TNF-alpha leading to significant reduction in nephrotoxicity along with reduction in the level of IL-6, IL-8 with increase in IL-10. Histopathological findings justified the toxicity to kidney tissues in cisplatin treated groups whereas raloxifene pre-treated group ameliorated the condition.

Present study was carried out to study effect of raloxifene on cisplatin induced nephrotoxicity which is dose limiting side effect and is confirmed by many preclinical studies. Pre-treatment of raloxifene prevented cisplatin's nephrotoxicity to some extent. Cisplatin has been reported to cause its nephrotoxicity through the activation of nuclear factor κB (NFκB) that triggers the release of various proinflammatory cytokines like tumour necrosis factor alpha (TNF-α), interleukin 6 (IL-6) and interleukin 1 beta (IL-1β) and reduce the level of interleukin 10 (IL-10) [8, 29–31]. Cisplatin control group increased the level of TNF-α, IL-6 and IL-1β. Moreover, cisplatin augmented serum level of creatinine, blood urea nitrogen (BUN) and albumin which are the biomarkers indicating damage to the kidney tubules. However, pre-treatment of raloxifene significantly decreased the level of TNF-α, IL-8, IL-6 and increased IL-10. There was decline in the serum creatinine and blood urea nitrogen level in pre-treated group compared to cisplatin control group. These results were justified with the help of Histopathological studies.

Significant positive association was found between raloxifene and cisplatin that is evident from reduced kidney damage and improved breast cancer status. The pre-treatment of raloxifene showed decreased levels of BUN and creatinine and increased level of albumin when compared to cisplatin treated rats. Moreover, treatment raloxifene and cisplatin markedly decreased inflammation which is evident from decreased level of p65 subunit of NF-kB along with level of other proinflammatory cytokines like TNF-alpha, IL-6. The treatment with raloxifene and cisplatin retarded the cell proliferation thereby decreased the tumour volume and increased the % survival when compared to the cisplatin treated rats. Despite the preponderance of both drugs as sole agents for anti-neoplastic effect, the combinatorial aid of both drugs seems to abate the tumour volume by reducing cell proliferation to an appreciable extent.

In conclusion, these data demonstrate that pre-treatment of raloxifene showed amelioration in cisplatin induced nephrotoxicity as decreased tumour size significantly. These findings suggests the use of this combination for further analysis using different animal model and carcinogens, so that it can be introduced into the clinical trials for human testing.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests or conflict of interests.

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