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Evaluation of *Terminalia arjuna* in Comparison to Taurine against Experimental Nephrotoxicity due to Cisplatin in Rats

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ABSTRACT

Background: Cisplatin is one of the most remarkable solutions in 'the war on cancer'. Although cisplatin has been a mainstay for cancer therapy, its use is mainly limited by nephrotoxicity. The current study was aimed to evaluate the ameliorative potential of *Terminalia arjuna* (TA) in comparison to taurine against cisplatin toxicity.

Methods: A total of 36 male *Wistar* rats were divided into 6 groups of 6 rats in each. Group 1 was normal control. Cisplatin @ 5 mg/kg b.wt was injected on day 1 to groups 2, 5 and 6. Aqueous leaf extract of *Terminalia arjuna* was administered orally @ 400 mg/kg b. wt to groups 3, 5 and Groups 4, 6 recieved taurine orally @ 1000 mg/kg b.wt for 14 days. Blood samples were collected from animals to assess Kidney function tests, oxidative stress and cytokines and renal tissues were examined for histological changes, if any.

Result: Antioxidant profile, serobiochemical and cytokine parameters were significantly ($P<0.05$) increased and histopathological studies revealed degenerative changes and marked infiltration in the kidney of group 2 when compared to groups 1, 3 and 4. However, These changes were reversed in groups 5 and 6 that were administered with *Terminalia arjuna* and taurine, respectively. In conclusion, the results of the present investigation elucidated that both *Terminalia arjuna* and taurine have potent nephroprotective activity in cisplatin injected *Wistar* rats.

Key words: Cisplatin, Nephrotoxicity, Taurine, *Terminalia arjuna.*

INTRODUCTION

Cisplatin is a highly effective and widely used anti-neoplastic drug against various solid tumors (Erhan *et al*. 2019). The anticancer behaviour of cisplatin originates from its ability to bind to N-7 of purine bases of cellular DNA, which leads to formation of mono-adducts that are transformed into inter-strand cross links and intra-strand cross links by reaction of second reactive site of the drug with the second nucleobase (Waseem *et al*. 2014). Despite being a potent anticancer drug, cisplatin elicits dose and time dependent nephrotoxicity limiting its clinical utility in 25–35% of hospitalized patients undergoing chemotherapy (Ramya *et al*. 2013).

The mechanisms by which cisplatin exerts its cytotoxic effects involve inflammation, oxidative stress and apoptosis (Abdel Daim *et al*. 2019). Cisplatin becomes highly reactive within the cell and conjugates with molecules such as DNA. Intra- and inter-strand cross-linking of DNA by cisplatin blocks DNA replication and gene transcription. Thus, DNA damage is a critical component of toxicity. Due to its low molecular weight and uncharged character, unbound cisplatin in the plasma is freely filtered by the glomerulus. Most of the cisplatin is trapped within the renal cortex (Launay-Vacher *et al*., 2008). The concentration of cisplatin in the proximal tubular cells is 5 times higher than the serum concentration and thus such an accumulation of cisplatin in kidney contributes to its nephrotoxicity (Ozkok and Edelstein, 2014).

Medicinal plants play a very important role in primary health-care system. According to WHO, 60% of the world's population relies on herbal medicine. TA is an ayurvedic plant with important medicinal value. It is commonly known as Arjuna, which belongs to family Combretaceae (Amalraj and Gopi, 2017). Medicinal properties of TA include antioxidant, anti-inflammatory, anti-carcinogenic and gastro-protective effects (Verma and singh 2013). The aqueous extract of TA possesses protective action against renal dysfunction by antioxidant mechanism with enhanced levels of GSH activity, decreased level of LPO (Manna *et al.,* 2006). As a consequence of these properties, TA can have immense potential in preventing

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the oxidative damage produced by cisplatin (Sherif, 2015).

Taurine is the major intracellular sulphur containing ß-amino acid with diverse cytoprotective activity and is important for the regular functioning of organs (Brosnan and Brosnan, 2006). It plays a major role in bile acid conjugation, osmoregulation, cell proliferation and prevention of oxidant-induced injury in many cells (Bouckenooghe *et al.,* 2006). Taurine treatment inhibits oxidative stress and apoptosis. Taurine also exerts nephroprotective effects, due to its antioxidant and membrane stabilization effects (Han and Chesney, 2012). Objectives of investigation are to study the nephrotoxicity due to cisplatin and to evaluate and compare nephroprotective potential of TA with taurine.

MATERIALS AND METHODS

Chemicals

All chemicals were of analytical grade and they are obtained from Qualigens Pvt. Ltd., Mumbai and SRL Pvt. Ltd., Mumbai, India.

Plant material and preparation of leaf extract

The fresh leaves of TA plant were collected from Hyderabad, India. The plant species were authenticated by Scientist, Agricultural College, Hyderabad, India. Those leaves were washed and dried at room temperature for 40 days and then powdered using a mechanical blender. Then, 1gram powder was mixed with 100 ml of boiled distilled water and stirred on hot plate for 20 minutes. Thereafter, extract was filtered through Whatman No.1 filter paper. It was kept at 4°C for further use (Raj *et al.* 2020).

Animals and experimental design

This experiment was conducted in November 2020, at College of Veterinary Science, PVNR TVU, Hyderabad, Telangana, India. Total of 36 male *Wistar* rats aged about 90 days with an average body weight of 170 ± 10 g were obtained from Vyas labs, Hyderabad. They were divided into 6 equal groups (n=6) with different treatments (Table 1) and were housed in polypropylene cages, under controlled environmental conditions. The animals were maintained on standard balanced diet with drinking water *ad libitum*. All the experimental procedures and protocols used in this study were reviewed and approved by the IAEC (No.5/22/C.V.Sc., Hyd. IAEC- Rats/29.02.2020) and were in accordance with the guidelines of the CPCSEA.

Table 1: Experimental design with group-wise treatment protocol.

Group	Treatment	No.of Animals
1.	Normal saline for 14 days	6
2.	Cisplatin @ 5 mg/kg bodyweight intraperitoneally on day 1	6
3.	Aqueous leaf extract of *Terminalia arjuna* (TA) @ 400 mg/kg bodyweigh torally for 14 days.	6
4.	Taurine @ 1000 mg/kg bodyweight orally for 14 days.	6
5.	Cisplatin (5 mg/kg b.wt, i.p) injection on Day 1+ Aqueous leaf extract of *Terminalia arjuna* (TA) @ 400 mg/kg body weight was orally administered for 14 days.	6
6.	Cisplatin (5 mg/kg, i.p) injection on Day 1+ Taurine @ 1000 mg/kg b.wt was orally administered for 14 days.	6

Blood collection

After completion of experiment, the blood samples were collected on last day of study from retro-orbital plexus of experimental rats for analysis. Then, the animals were euthanized and kidney tissues were collected immediately and kept in ice cold phosphate buffer. A small portion of the kidney was homogenized with tissue homogenizer to make 10% homogenate to assay the tissue antioxidants. Pieces of tissues from kidney were immediately kept in 10% of formalin fixative to study histological alterations.

Biochemical analysis

BUN and serum creatinine were estimated by kits from ERBA diagnostics Ltd, Surat, India. Malondialdehyde has been identified as the product of lipid peroxidation that reacts with thiobarbituric acid to give a red compound absorbing light maximally at 535 nm. GSH was estimated on the reaction of reduced glutathione with 5-5' dithiobis-2-nitrobenzoic acid to give a compound that absorbs light at 412 nm. Protein carbonyls were estimated based on the reaction of amino carbonyls with 2, 4-dinitrophenyl hydrazine to form hydrazones, which can be detected spectrophotometrically at 372 nm.

Quantitative sandwich enzyme immunoassay technique is followed to analyze TNF –*alpha* and IL-10. The ELISA kits were procured from Krishgen Bio systems, Mumbai, India.

Histology

For light microscopy examination, the formalin fixed kidney tissues were dehydrated through ascending grades of alcohol, cleared in three changes of xylene and were embedded in paraffin. Kidney sections each of 4 micron thickness were cut and stained with H and E stain.

Statistical analysis

Data were subjected to statistical analysis by applying one-way ANOVA usingthe SPSS; version 21. Differences between means were tested using Duncan's multiple comparison testand significance was set at $P < 0.05$.

RESULTS AND DISCUSSION

The results obtained in the present experiment are presented as below.

Sero-biochemistry

The concentration of BUN and serum creatinine (mg/dl) in group 2 (96.81 ± 0.11 and 1.49 ± 0.035, Respectively) was

Table 2: BUN (mg/dl), Creatinine (mg/dl),GSH (nm/mg protein), TBARS (nm/mg protein), Protein carbonyls (nm/mg protein), in different groups of rats

Group	BUN	Creatinine	GSH	TBARS	PC
1.Normal Control	36.69 ± 0.15 ^{c}	0.69 ± 0.025 ^{d}	37.19 ± 0.13 ^{a}	9.94 ± 0.09 ^{d}	3.88 ± 0.12 ^{c}
2.Cisplatin Control	96.81 ± 0.11 ^{a}	1.49 ± 0.035 ^{a}	17.41 ± 0.12 ^{d}	18.18 ± 0.12 ^{a}	9.71 ± 0.09 ^{a}
3.TA	37.10 ± 0.17 ^{c}	0.78 ± 0.029 ^{c}	35.97 ± 0.14 ^{b}	10.70 ± 0.14 ^{c}	4.23 ± 0.04 ^{c}
4. Taurine	37.00 ± 0.20 ^{c}	0.76 ± 0.023 ^{cd}	36.01 ± 0.11 ^{b}	10.96 ± 0.06 ^{c}	4.16 ± 0.18 ^{c}
5. Cisplatin + TA	53.13 ± 0.12 ^{b}	0.88 ± 0.017 ^{b}	28.54 ± 0.18 ^{c}	12.54 ± 0.08 ^{b}	5.97 ± 0.10 ^{b}
6. Cisplatin + Taurine	52.98 ± 0.14 ^{b}	0.83 ± 0.014 ^{bc}	28.95 ± 0.17 ^{c}	12.23 ± 0.23 ^{b}	6.08 ± 0.16 ^{b}

Values are mean±SE (n=6); one way ANOVA. Means with different alphabets differ significantly (P <0.05).

Table 3: TNF-*alpha* (pg/mg tissue) and IL-10 (pg/mg tissue) in different groups of rats.

Group	TNF	IL-10
1.Normal Control	7.80 ± 0.07 ^{d}	9.32 ± 0.08 ^{c}
2.Cisplatin Control	22.35 ± 0.24 ^{a}	14.95 ± 0.26 ^{a}
3.TA	8.97 ± 0.15 ^{c}	9.80 ± 0.14 ^{c}
4. Taurine	9.29 ± 0.11 ^{c}	9.47 ± 0.18 ^{c}
5. Cisplatin + TA	11.04 ± 0.21 ^{b}	12.06 ± 0.21 ^{b}
6. Cisplatin + Taurine	11.11 ± 0.17 ^{b}	12.23 ± 0.19 ^{b}

Values are mean±SE (n=6); one way ANOVA. Means with different alphabets differ significantly (P <0.05).

significantly (P < 0.05) higher when compared to non toxic groups 14th day, while treatment groups 5 (53.13 ± 0.12 and 0.88 ± 0.017, Respectively) and 6 (52.98 ± 0.14 and 0.83 ± 0.014, Respectively) showed significantly (P < 0.05) lower values in comparison to group 2 (Table 2).

Antioxidant profile

The concentration of GSH (nm/mg) revealed a significant (P < 0.05) decrease in toxic control group 2 (17.41 ± 0.12) when compared to non toxic groups, whereas treatment groups 5 and 6 (28.54 ± 0.18 and 28.95 ± 0.17, respectively) revealed a significant (P < 0.05) improvement as compared to toxic control group 2 (Table 2).

The concentration of TBARS and protein carbonyls (nm/mg) revealed a significant (P < 0.05) increase in toxic control group 2 (18.18 ± 0.12 and 9.71 ± 0.09) when compared to non toxic groups, whereas treatment groups 5 (12.54 ± 0.08 and 5.97 ± 0.10, Respectively) and 6 (12.23 ± 0.23 and 6.08 ± 0.16, Respectively) showed significantly (P < 0.05) lower values in comparison to group 2 (Table 2).

Cytokine profile

The concentration of TNF-α and IL-10 (pg/mg tissue) revealed a significant (P < 0.05) increase in toxic control group 2 (22.35 ± 0.24 and 14.95 ± 0.26, Respectively) when compared to non toxic groups, whereas treatment groups 5 (11.04 ± 0.21and 12.06 ± 0.21, Respectively) and 6 (11.11 ± 0.17 and 12.23 ± 0.19, Respectively) showed significantly (P < 0.05) lower values in comparison to group 2 (Table 3).

Histopathology

Normal histology of the rat kidney tissue was found in the non toxic groups (Fig 1). Renal tissue sections from rats treated with cisplatin showed moderate variations in glomerular structure (Fig 2), mild increase in bowman's space with significant shrinkage of some glomerular tufts, degenerations in glomerular capsule and mononuclear cell infiltration with moderate peritubular inflammation (Fig 3). The kidney tissue sections of the cisplatin treated rats exhibited marked acute tubular necrosis and marked dilation and degenerations of tubules and vacuolation (Fig 4), whereas rats treated with TA justified the protective action by minimizing the inflammation of mononuclear cells, tubular necrosis (Fig 5) and by showing mild tubular degenerative changes (Fig 6). Renal histology in taurine treated group showed mild infiltration of inflammatory cells (Fig 7) and congestion (Fig 8).

The present study was conducted on 3 month old *Wistar* rats for a period of 14 days to evaluate the protective role of TA and taurine against cisplatin induced nephrotoxicity. The biochemical markers, oxidative stress and cytokines were assessed. Histopathology of kidney tissues were conducted to draw possible conclusions at the end of the experiment. The increase in kidney biomarkers is observed in toxic group due to exposure to cisplatin is a function of the overall balance between the degree of oxidative stress and the antioxidant capability (Hosseinian *et al.* 2016). Rashed *et al.* (2011) also reported the elevation of serum creatinine and BUN following cisplatin injection. This is a clear indication of renal toxicity caused by cisplatin as the markers are released by the damaged kidney into circulatory system. In the study of Sherif (2015), administration of TA had a protective effect leading to improvement in renal function as indexed by marked decline in serum creatinine and BUN in comparison to cisplatin group. Marked recovery was observed in the markers after treatment with TA and taurine The antioxidant system is responsible primarily for defense against ROS, and the formation and elimination of ROS in the cells is accomplished by the radical scavenging system, which includes GSH, TBARS and protein carbonyls (Ekinci Akdemir *et al.* 2017). Karimi *et al.* (2018) reported increased MDA levels and decreased GSH levels in cases of cisplatin induced toxicity. Oxidative stress caused by cisplatin induced excessive production of ROS leads to peroxidation of membrane lipids and depletion of antioxidant enzymes. NADPH oxidase is an enzyme system, which enhances cisplatin mediated ROS generation and cytotoxicity (El

Sawalhi and Ahmed, 2014). Lipid peroxidation causes glomerular injury, increases fluidity and permeability of tubular membranes and triggers hypertrophy of renal tubules (Al Kahtani *et al.* 2014). The natural antioxidant arjunolic acid was shown to improve cisplatin induced nephrotoxicity via significant enhancement of antioxidant activity of renal GSH and significant reduction of renal MDA levels (Sherif, 2015; Elsherbiny *et al.* 2016). Our findings revealed that TA and taurine administration increased GSH levels, suppressed the increase in MDA and protein carbonyls concentration observed in cisplatin group.

Inflammation plays a crucial role in the pathogenesis of cisplatin induced nephrotoxicity (Zhang *et al*. 2007). TNF-α plays a key role in mediating the inflammatory injury in cisplatin-induced toxicity (Yousef and Hussien, 2015). Concurrent with the induction of a stress-activated inflammatory response, many agents with anti-inflammatory properties are generated that may inhibit tissue damage

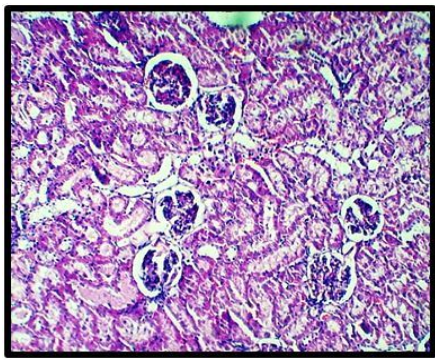

Fig 1: Photomicrograph of kidney tissue showing normal architecture of Glomerulus and tubules (Group 1) H and E X 100

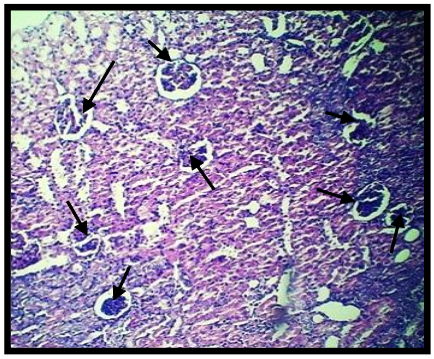

Fig 2: Photomicrograph of kidney tissue showing moderate variations in glomerular structure includes atrophied and degenerated glomerulus (Group 2) (thin arrow) H and E X100

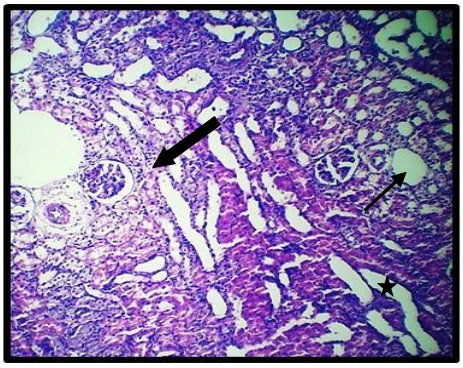

Fig 3: Photomicrograph of kidney tissue showing vacant glomeruli (thin arrow), distorted and elongated tubules (star) and moderate peritubular inflammation (thick arrow) with moderate tubular degenerations (Group 2) H and E X100

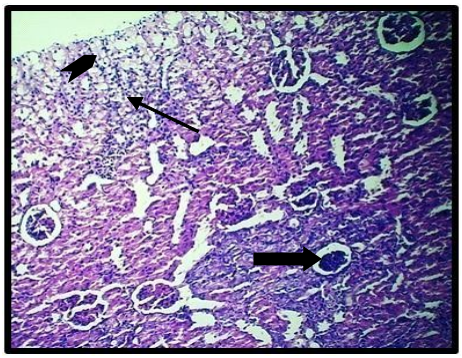

Fig 4: Photomicrograph of kidney tissue showing mild tubular vacuolation (thin arrow), moderate to marked inflammation (arrow head) and glomerular degeneration (thick arrow) (Group 2) H and E X100

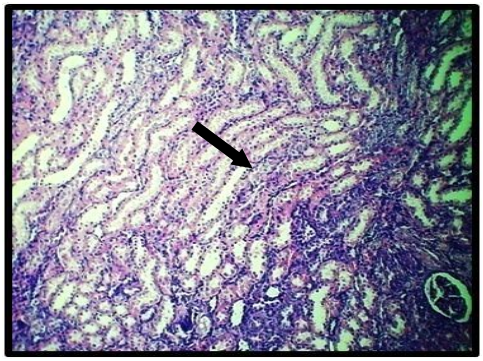

Fig 5: Photomicrograph of kidney tissue showing mild acute tubular necrosis and inflammation (thick arrow) (Group 5) H and E X100

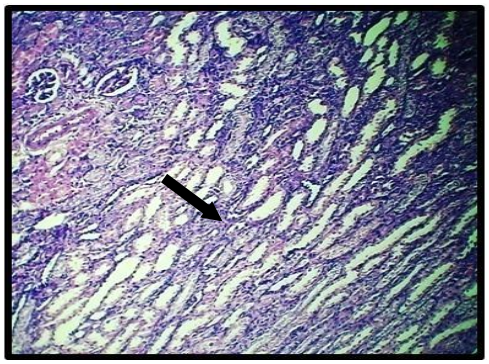

Fig 6: Photomicrograph of kidney tissue showing mild tubular degeneration and inflammatory changes (thick arrow) (Group 5) H and E X100.

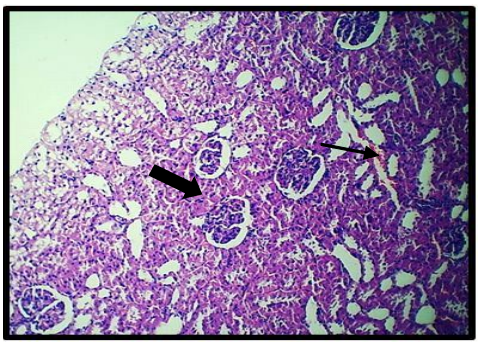

Fig 7: Photomicrograph of kidney tissue showing mild inflammation (thick arrow) and mild congestion (thin arrow) (Group 6) H and E X100

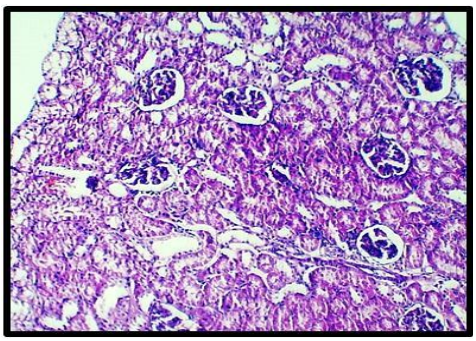

Fig 8: Photomicrograph of kidney tissue showing normal structure of glomerulus and tubules with mild inflammation (Group 6) H and E X100

(Deng *et al*. 2001). IL-10 is a multifunctional anti-inflammatory cytokine that has been reported to attenuate different renal pathologies (Kitching *et al*. 2002). TA and taurine at the doses administered significantly normalized the elevated levels of inflammatory cytokines and thus protected the kidney from inflammatory insult.

These results are further substantiated from histopathology, which revealed normal histology of a rat kidney tissue found in control group. However, histopathology of renal tissue sections from rats treated with cisplatin alone showed shrunken glomeruli, mononuclear cell infiltration, including acute tubular necrosis and marked dilation of proximal convoluted tubules. The cisplatin-induced histological alterations are in agreement with previous studies (Athira *et al*., 2016 and Malik *et al*., 2016). TA and taurine administration for 14 days significantly improved the cisplatin induced histological changes and showed minimum tubular damage, less necrotic damage and less accumulation of inflammatory cells.

CONCLUSION

In conclusion, the study revealed that cisplatin induces nephrotoxicity by oxidative stress, thus impairing the sero-biochemical parameters and histoarchitecture of kidney. The treatment with TA and taurine showed significant improvement in the function of kidney tissue protection and improvements in cisplatin induced toxicity due to the presence of marked antioxidant potential.

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