

Nephroprotective effect of biocurcumin and phyllanthus emblica in cisplatin-induced renal injury in rats

Ankita Negi¹, Bhupinder Singh Kalra¹, Akhilesh Mishra¹, Shramana Mandal², Shalini Chawla^{1*}

1.Department of Pharmacology Maulana Azad Medical College, New Delhi-110002

2.Department of Pathology Maulana Azad Medical College, New Delhi-110002

* Corresponding author: Dr. Shalini Chawla , Email: chawlashalini45@gmail.com



Ankita Negi
Pharmacologist

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Abstract

Background- Cisplatin is the most commonly used anticancer agent in treating many tumours. It has been postulated that oxidative stress is responsible for cisplatin-induced nephrotoxicity. The present study aimed to evaluate the reno-protective effects of *Biocurcumin* and *Phyllanthus emblica* in cisplatin-induced renal injury in rats.

Methods- The study was conducted in SD rats for 7 days. Total of 35 rats were divided into 5 groups. Group I received normal Saline throughout the study. Group II received a single dose of cisplatin on the 4th day (20mg/kg). Group III, group IV and group V received bio-curcumin (100 mg/kg), *phyllanthus emblica* (300mg/kg) and a combination of both plant extract orally for 7 days and a single dose of cisplatin on 4th day. Rats were euthanized with an overdose of thiopental sodium, blood and tissue samples were collected for assessment on the 8th day. Renal injury was assessed by serum creatinine and BUN. SOD and catalase were assessed by ELISA in renal tissue. The degree of severity of renal tissue was assessed by histopathology.

Results- It was observed that biocurcumin and phyllanthus emblica extracts significantly ($p<0.05$) attenuate renal damage by decreasing serum creatinine and BUN. It significantly enhances the activities of catalase and SOD—a single dose of cisplatin results in marked inflammation, protein cast, and cellular swelling. But, in groups treated with plant extract along with cisplatin above histopathological changes were not observed.

Conclusion- concluded that *plant extracts* ameliorate renal damage caused by cisplatin may be due to its antioxidative properties.

1. Introduction

Kidney damage is a sudden decline in kidney function that includes injury and impairment. It is a common medical problem in both developed and developing nations(1). There are many causes of kidney injury like drugs, sepsis, hypovolemia etc. If not treated it can cause many complications(2,3). Cisplatin is one such

drug that causes renal injury. One of the major mechanisms of cisplatin-induced nephrotoxicity is oxidative stress. Cisplatin therapy causes excess reactive oxygen species (ROS) generation and antioxidant system depletion. Reactive oxygen species are highly reactive and unstable molecules. This molecule can damage and change cellular components like lipids, proteins, and DNA, causing cellular stress(4).

Some known plants do possess renoprotective potential against oxidative stress. *Curcuma longa* (Curcumin) and *Phyllanthus Emblica* are medicinal plants which have diverse pharmacological effects and anti-inflammatory and antioxidant capabilities. They protect against nephrotoxicity(5). Curcumin, is a yellow pigment found in the rhizome of turmeric (*Curcuma longa* L. Zingiberaceae)(6). Turmeric is much more commonly available as a dried powder in Indian kitchens(7). It has a wide range of biological actions including antibacterial, anti-inflammatory, antiepileptic, and antioxidant properties. Curcumin can subtly increase the expression of antioxidant proteins including catalase (CAT) and superoxide dismutase (SOD). It has been utilised for its renoprotective cardio-protective, hypoglycaemic etc(8). Curcumin has a low bioavailability, which is one of its main disadvantages(9). Curcuminoids, obtained from the rhizomes of *Curcuma longa* L., Zingiberaceae (turmeric), are the most commonly utilized phytonutrients in the food sector and have recently gained popularity for their therapeutic properties(10). Purified curcuminoids are typically combined with turmeric essential oil to increase the bioavailability of the curcuminoids (11). Biocurcumin is a nutraceutical product. It contains a curcumin-essential oil complex mixture with Ar-turmerone which is the essential oil of turmeric, thereby increasing its bioavailability. The half-life of bio curcumin is 5 hours. The time to achieve the maximum concentration is 3.4 hours (12).

Phyllanthus Emblica is known as Amla (Indian Gooseberry) and is a member of the Euphorbeaceae family(13). *Phyllanthus Emblica* L. (syn. *Emblica Officinalis*) has long been utilised as an edible plant as well as for its medicinal properties. All parts of *P. emblica* had therapeutic properties, particularly its fruits. It contains a higher amount of vitamin C and higher concentrations of most minerals, proteins and amino acids like glutamic acid, proline, aspartic acid, gallic acid, alanine, cystine and lysine. It contains a higher amount of hydrolysable tannins like emblicanin A and B(14). Its pharmacological report revealed its antioxidant, antimicrobial, anti-inflammatory, antipyretic and analgesic(15).

The main reason for its anti-oxidant properties is the ascorbic acid, tannins, and polyphenolic contents of *Phyllanthus Emblica*. Gallic acid is a pow-

erful antioxidant with a strong free radical scavenging ability(16,17). Thus, the present study aimed to evaluate the reno-protective effect of biocurcumin and *phyllanthus emblica* individually as well as in combination with cisplatin-induced nephrotoxicity.

2 Materials and Methods

2.1 Animals

35 Sprague Dawley rats of 6 to 8 months old, weighing 200-300g, either sex were used. Rats were housed in polypropylene cages at the temperature of $18\pm 26^{\circ}\text{C}$ with 12 h light: dark cycle respectively. They were provided with chow food and water. This study was conducted in the Department of Pharmacology using the animal facility of Maulana Azad Medical College with the approval of the Institutional Animal Ethics Committee (IAEC) approval number EC/2021/03.

2.2 Chemicals

Cisplatin was purchased from a central store, Lok Nayak Hospital, Delhi. It's used for the induction of renal injury. Biocurcumin was obtained from Livlong nutraceuticals limited a subsidiary company of Arjuna Natural Extract Limited, Kerala, India. *Phyllanthus emblica* obtained from Arjuna Natural Limited, Kerala, India. The oxidative stress biomarkers like superoxide dismutase and catalase ELIZA kit were purchased from Purchases from G-Biosciences 9800, Page Avenue, St. Louis, MO, USA.

2.3 Experimental design

Sprague Dawley rats were divided into 5 groups containing 7 animals. Before the experiment, all the rats were acclimatized for a period of 7 days. The total duration of the experiment was 7 days.

Group 1 served as the control group and received normal saline (1ml/kg) for 7 days.

Group 2 received a single dose of cisplatin [20 mg/kg body weight, intraperitoneally (i.p.)] on the 4th day.

Group 3 received Bio curcumin (100mg/kg body weight, orally, for 7 days) + cisplatin (20mg/kg body weight, i.p, on the 4th day).

Group 4 received *Phyllanthus Emblica* (300mg/kg body weight, for 7 days+ cisplatin (20mg/kg body

weight, i.p on the 4th day).

Group 5 received Biocurcumin(100mg/kg) + Phyllanthus Emblica(300mg/kg) + cisplatin (20mg/kg).

Curcumin and Phyllanthus Emblica were suspended in DMSO (dimethyl sulfoxide). At the end of the experiment (i.e. 8th day of the experiment), animals were euthanized with an overdose of thiopental sodium (100mg/kg, i.p).

2.4 Collection of blood

1) For assessment for renal function test

Blood was collected on day 0 from the tail vein of each rat. On the 8th day, rats were euthanised and blood was collected by cardiac puncture. 18 Total 2ml of blood was collected, kept in an Eppendorf tube (2ml) and processed for serum separation by centrifuging the blood samples at 4000 rpm for 10 minutes. The serum was stored at -200C and later was analysed for biochemical tests.

Biochemical test: The renal function test was determined by assaying blood urea nitrogen (BUN) and serum creatinine, BUN and creatinine concentration were measured by Urea assay Kit and Creatinine assay kit.

2) Assessment of Oxidative Stress

For assessment of oxidative stress, animals were sacrificed by overdose of thiopental sodium (100mg/kg). Then the rat's abdominal and thoracic cavities were opened, exposing the kidney tissue. After carefully cutting the adhesive tissue, kidney tissue was removed, washed with Phosphate buffer saline and homogenized along with PBS in a tissue homogenizer. Homogenates were centrifuged at 3000 rpm for 20 minutes. The supernatant was collected carefully and stored at -200C for analysis of superoxide dismutase and catalase activity.

Estimation of free radical scavenging enzyme: The activities of superoxide dismutase (SOD), and catalase (CAT) were assessed.

3) Histopathological examination of the Kidney

Kidneys were removed 72 h after cisplatin injection and placed in 10% formalin. After cleaning, the kidney tissues were fixed in paraffin and sectioned. The paraffin-sectioned tissue was stained with haematoxylin and eosin (H&E) and was analysed. Slides were examined and assigned for the

severity of changes by an observer blinded to the treatments of the animals, using grades of none (-), mild (+), moderate (++), and severe (+++).

2.5 Statistical Analysis

Results were expressed as mean $\pm$ Standard Deviation. The intergroup variation was measured by one-way analysis of variance (ANOVA) followed by post hoc analysis using SPSS software version 25. Statistical significance is considered at $p \leq 0.05$.

3. Result

3.1 Effect of cisplatin (CIS), biocurcumin (BC) and Phyllanthus Emblica (PE) on serum creatinine and Blood urea nitrogen (BUN)

There was no significant change in serum creatinine and BUN in the control group from day 0 to day 8. The serum creatinine and blood urea nitrogen levels were significantly increased ($p < 0.05$) in the cisplatin-treated group from day 0 to day 8 (Figure 1 & 2). Serum creatinine and BUN were significantly increased in the cisplatin group compared to the control group. Groups treated with cisplatin+ BC reduced the elevated serum creatinine and BUN levels compared to cisplatin treated ($p < 0.05$) (Figure 1 & 2). Similarly, treatment with cisplatin + PE also reduced the elevated level of serum creatinine and BUN as compared to cisplatin. ($p < 0.05$) (Figure 1 & 2). In groups treated with BC and PE plant extracts when compared to the combination group (BC + PE + cisplatin) the difference in mean creatinine and BUN was found to be non-significant. (Figure 1 & 2)

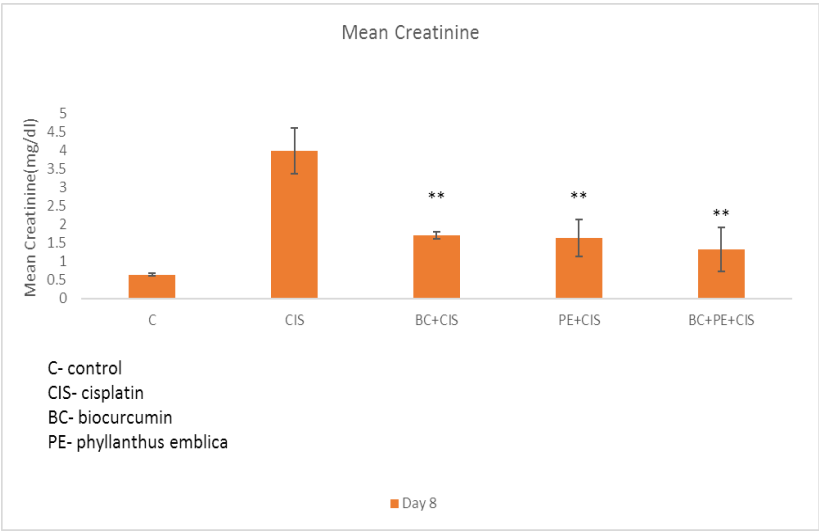


Figure 1. Mean serum creatinine of different groups.

*Statistically significant at $p < 0.05$ as compared to control.
**Statistically significant at $p < 0.05$ as compared to cisplatin

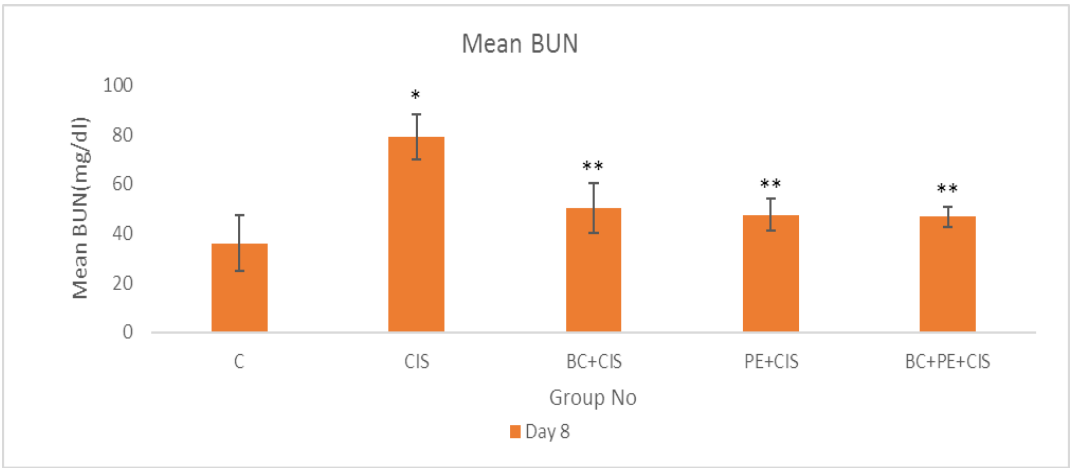


Figure 2. Mean blood urea nitrogen of different groups.

*Statistically significant at $p < 0.05$ as compared to control.
**Statistically significant at $p < 0.05$ as compared to cisplatin

in mean creatinine and BUN was found to be non-significant. (Figure 1 & 2)

3.2 Effect of cisplatin, biocurcumin (BC) and Phyllanthus Emblica (PE) on markers of oxidative stress.

The renal toxicity of cisplatin is mainly associated with the induction of oxidative stress, for this reason, various enzymatic antioxidant markers were measured. Cisplatin treatment significantly decreases ($p < 0.05$) the activities of various antioxidant enzymes (i.e. catalase, superoxide dismutase)

as compared to a control group (Figure 3 & 4). The effect of biocurcumin and phyllanthus emblica plant extract on the above markers of oxidative stress was as follows:

3.3 Effect of biocurcumin and Phyllanthus emblica on superoxide dismutase (SOD) and catalase (CAT)

The activity of superoxide dismutase and catalase was significantly high in groups treated with biocurcumin and Phyllanthus emblica ($p < 0.05$) compared to cisplatin-treated group in which the activity of this enzyme was dramatically reduced (Figure 3 & 4). In groups treated

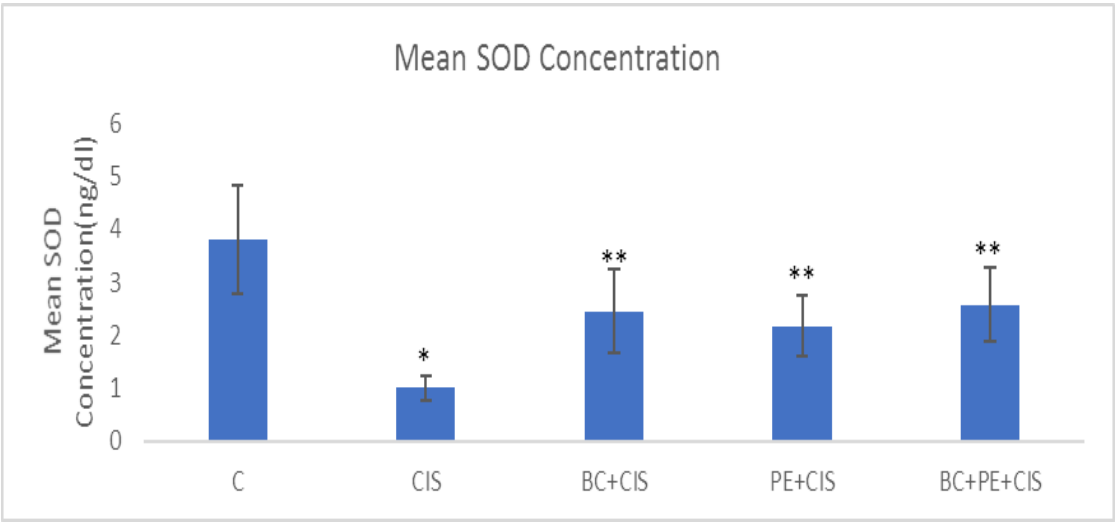


Figure 3. Mean renal superoxide dismutase (ng/dl) level of different groups.

*Statistically significant at $p < 0.05$ as compared to control.
**Statistically significant at $p < 0.05$ as compared to cisplatin

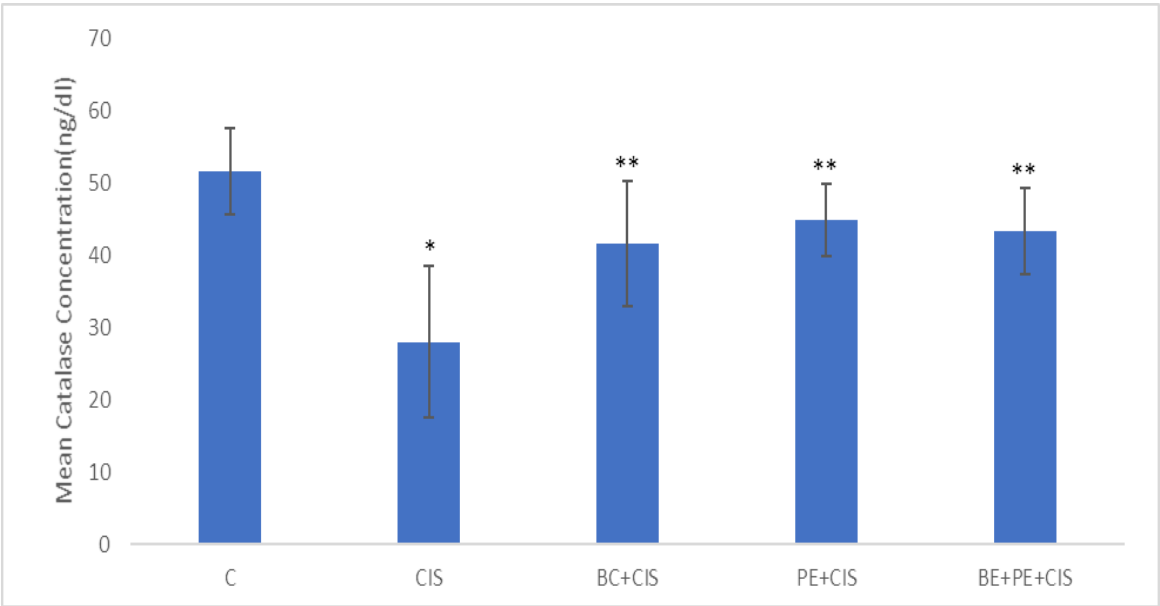


Figure 4. Mean catalase (ng/dl) of different group

*Statistically significant at $p < 0.05$ as compared to control.
**Statistically significant at $p < 0.05$ as compared to cisplatin

activity of this enzyme was dramatically reduced (Figure 3 & 4). In groups treated with biocurcumin and phyllanthus emblica when compared to the combination group (BC + PE + cisplatin) the difference in mean superoxide dismutase and catalase was found to be non-significant. This data suggest that physiological levels of superoxide dismutase and catalase were maintained in all the groups other than cisplatin-treated group.

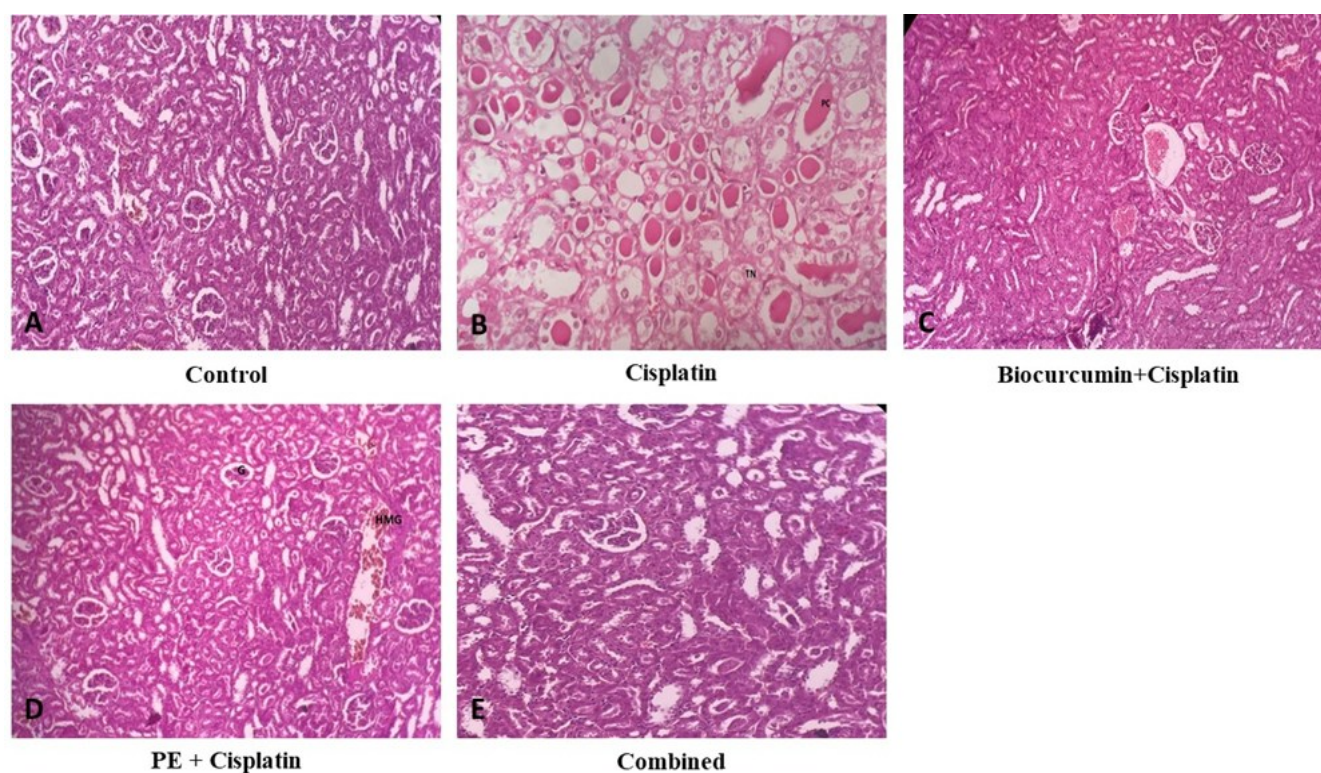
3.4 Histopathological examination of the kidney

H&E staining of kidney sections showed no morphological changes in the control group. By contrast, rats treated with cisplatin showed marked tubular injury including hydropic degeneration, cast, inflammation and haemorrhage and tubular necrosis, cellular swelling (Table 1). While groups treated with BC+ cisplatin, PE + cisplatin group and combination group (BC + PE + Cisplatin) showed marked morphological improvement of renal tissue (Figure 5A, B, C, D & E).

Table 1: Representation of score for the severity of changes in different groups

<u>Group</u>	Hydropic de- generation	Cast	Inflamma- tion/ Haemor- rhage	Tubular necrosis
Control	—	—	—	—
Cisplatin	+++	+++	+++	+++
BC + CIS	—	—	++	—
PE + CIS	—	—	++	—
Combined (BC + PE + CIS)	—	—	—	—

#Grades for none (-), mild (+), moderate (++), and severe (+++)

**Figure 5.** A: Control Group; B: Cisplatin Group; C: BC+ Cis; D: PE + Cis; E: Combined group

Abbreviations: G- glomerulus, PT- Proximal tubules, DT- Distal tubules, BC- Bowman's capsule; TN- tubular necro-

4. Discussion

Excretion and concentration of harmful metabolites play a key role in the kidney. Drug-induced nephrotoxicity is a major concern in clinical medicine. Cisplatin is one such drug that causes nephrotoxicity. The most prominent known pathway contributing to cisplatin-induced nephrotoxicity is oxidative stress.⁴ Some herbal extracts have shown promising results against drug-induced nephrotoxicity.

The present study was planned to evaluate the nephroprotective and antioxidant activity of biocurcumin and phyllanthus emblica in cisplatin-induced renal injury in rats. In this study, a single dose of cisplatin (20mg/kg) was administered intraperitoneally to Sprague Dawley rats which is in accordance with the previous study. It was observed in previous studies that a single high dose of cisplatin in rats resulted in minor alterations and morphological alterations.¹⁹ Cisplatin accumulates in renal cells causing nephrotoxicity. To counteract this nephrotoxicity, we have used herbal plant extracts like biocurcumin and phyllanthus emblica.^{20,21}

In our study, we observed that in the group treated with cisplatin, there was a significant increase in serum creatinine and BUN from baseline to day 8. ($p < 0.05$) and a significant reduction in SOD and catalase. This is indicative of renal injury. Cisplatin therapy causes excess reactive oxygen species (ROS) generation and antioxidant system depletion.²² This results in reduced creatinine clearance, increased production of hydrogen peroxide and reduced antioxidant capacity.¹⁹ Due to extensive morphological damage and functional impairment, the kidneys fail to remove nitrogenous wastes from the blood. Hence, BUN and uric acid accumulate in the blood.²³ BUN and serum creatinine are the most commonly used metabolites as indicators in rodents to diagnose nephrotoxicity.²⁴

We observed that the group treated with biocurcumin with cisplatin and phyllanthus emblica with cisplatin exhibited a significant reduction in serum creatinine and BUN when compared to the group treated only with cisplatin. In our study, significant

elevation in superoxide dismutase and catalase was observed in groups treated with biocurcumin and phyllanthus emblica when compared to the group treated only with cisplatin. No significant inter-group variation was observed in biocurcumin, phyllanthus emblica and combination group, which is compared with previous studies indicative of prevention of cisplatin-induced damage to the kidney. The only difference between curcumin and biocurcumin is that curcumin has low bioavailability compared to biocurcumin. Purified curcuminoids are combined with turmeric essential oil to increase bioavailability.¹³

Curcumin substance exerts an antioxidant effect. It can remove superoxide anion (O_2^-) hydroxyl radicals (OH) H_2O_2 , singlet oxygen, nitric oxide, peroxynitrite, and peroxy radicals (ROO) from the body.²⁵ The oxidative damage caused by H_2O_2 is prevented in renal tubule epithelial cells by curcumin.²⁶ In a study, in one group, a single dose of cisplatin (5mg/kg), 2nd group received 60 mg/kg of curcumin only for 5 days and the rest of the groups received 15, 30 and 60 mg/kg of curcumin 2 days before and 3 days after cisplatin. It was observed that a single dose of cisplatin significantly increased the serum creatinine and blood urea nitrogen and curcumin treatment significantly and dose-dependently prevented this rise in serum creatinine and BUN.⁶ The only difference was that we used a higher dose of cisplatin and instead of curcumin we used biocurcumin. Our findings are in concordance with a previous study which was done by Hashish et al, they observed that curcumin 80mg/kg was administered to prevent copper-sulphate-induced oxidative stress renal injury. It was observed, that the group treated with curcumin significantly increased the superoxide dismutase and catalase compared to the group treated with copper sulphate.²⁷

Phytoconstituents of *phyllanthus emblica* have antibacterial, antioxidant, antidiabetic, hypolipidemic, anticancer, hepatoprotective and nephroprotective potential and play a significant role in ameliorating oxidative stress¹⁶ Administration of *phyllanthus emblica* extract significantly enhanced the activities of enzymes (SOD and catalase) thereby, ameliorating the toxic effect of cisplatin on renal cells. Our study is in accordance with a previous study done by Kalra et al. Three different doses of *phyllanthus emblica* 50mg/kg, 100mg/kg and 200mg/kg were used to see its effect on oxidative stress induced by cisplatin It was observed that groups treated with *phyllanthus emblica* extract showed a significant reduction in serum creatinine, blood urea nitrogen and increase in superoxide dismutase and catalase compare to the rats treated with cisplatin.²⁸

In our study, we observed group treated with cisplatin showed severe morphological alteration like hydropic degeneration, tubular necrosis, protein cast, inflammation, haemorrhage and cellular swelling. The groups receiving both cisplatin and plant extracts showed slight cellular swelling and haemorrhage. In our study biocurcumin and *phyllanthus emblica* prevented these cisplatin-induced structural changes suggesting the possible involvement of reactive oxygen species (ROS). Our study supports the findings of Kuhad et al. who found necrosis, atrophy, and hyalin casts in the cisplatin group, whereas there was considerable morphological protection in the curcumin-treated group.⁶ Our study was also concurrent to Purena et al. found necrosis, cellular swelling, haemorrhage, and glomerulus degeneration in the cisplatin-treated groups, but no pathological changes in the *phyllanthus emblica* extract-treated groups. The groups receiving both cisplatin and plant extract showed slight necrosis and cellular swelling in renal tubules, as well as sloughing of Bowman's capsule and glomerulus degeneration.¹⁶

The main limitation of our study was that we have taken only one animal model and a single dose was selected rather than multiple doses. Only one mechanism was studied and no positive control was taken due to animal welfare considerations.

There is a need to study other mechanisms of biocurcumin and *phyllanthus emblica* like its inflammation, antiapoptotic etc.

5. Conclusion

The present study concluded that a single dose of cisplatin leads to significant renal damage as evidenced by impaired renal function, oxidative stress and histological changes. Administration of biocurcumin and *phyllanthus emblica* extract attenuates the toxicity of cisplatin in renal tissue by inhibiting oxidative stress. Further, it improved renal function and morphology. The combination of these plants was found to be insignificant suggestive of no additional benefit. Our result indicated the renoprotective potential of biocurcumin and *phyllanthus emblica* against cisplatin-induced renal damage.

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7. DECLARATIONS

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Conflict of interest: No Conflict of interest/ Nil

Ethical approval: IEC Registration no- ECR/329/Inst/DL/2013/RR-2019

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