DOI: https://doi.org/10.53350/pjmhs2115112951

ORIGINAL ARTICE

Effect of Ethanolic Extract of Carica Papaya seeds in Drug-Induced Acute Nephrotoxicity

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ABSTRACT

Background: Nephrotoxicity is characterized by raised serum urea and creatinine levels and kidneys being one of the primary organs of drug concentration and excretion are vulnerable to many widely used marketed drugs, including anti-cancer drugs, antibiotics, immunosuppressants, and radio contrast agents, are nephrotoxic.
Aim: To determine the nephroprotective effect of ethanolic extract of *Carica papaya* seeds in Aminoglycoside induced acute nephrotoxicity. **Study design**: Quasi Experimental study.
Methodology: Thirty Sprague Dawley rats were sub divided into 3 groups i.e., I, II and III with 10 rats in each group. Group II and III were administered Aminoglycoside drug; Gentamycin in 80 mg/kg) via intraperitoneal route once daily for 5 consecutive days to induce acute nephrotoxicity. At day 6, nephrotoxicity was confirmed by measuring serum urea and creatinine. Ethanolic extract of *Carica papaya* seeds (1000 mg/kg) was started once daily through oral route in group III for 5 consecutive days to see the nephroprotective effects of seed extract after causing acute kidney injury. All animals were given standard diet pellets manufactured at NIH.
Results: Mean serum urea and creatinine for Group I (Control Group) at day 0 were 24.90 mg/dL ± 1.633 and .750 mg/dL ± .0619 respectively. Mean serum urea and creatinine for Group II (Disease Control Group) was 81.00 mg/dL ± 1.247 and 1.980mg/dL ± .0467 at day 6th. This suggested induction of nephrotoxicity by Gentamycin. Mean serum urea and creatinine for Group III (Ethanolic Extract Treated Group) at 11 day was 72.40mg/dL± .991 and 1.680 mg/dL± .0467 after 5 days treatment with ethanolic extract of *Carica papaya* seeds.
Conclusion: We concluded that ethanolic extract of *Carica papaya* seeds has significant nephroprotective effects on Aminoglycoside induced acute nephrotoxicity in rats.
Keywords: COVID-19, Vaccination, Awareness and Adverse Effects.

INTRODUCTION

Exposure of drugs and different chemicals directly or indirectly can cause nephrotoxicity and may lead to acute or chronic renal failure[1,2]. In approximately 6% of admitted patients in hospitals, adverse reactions to drugs occur out of which approximately 7 % of patients suffer drug-related toxicities[3].

In critically ill patients, drugs that are nephrotoxic may be responsible for 19%–25% of acute kidney injury[4]. Kidneys being one of the primary organs of drug concentration and excretion are vulnerable to many widely used marketed drugs, including anti-cancer drugs, antibiotics, immunosuppressants and radiocontrast agents, are nephrotoxic[5].

Nephrotoxicity is characterized by raised serum urea and creatinine levels[6]. Aminoglycosides used for the treatment of Gram-negative bacteria have been a vital component of antibiotic armamentarium due to their cost-effectiveness and efficacy[7]. Aminoglycosides are eliminated unchanged in the urine by glomerular filtration[8] due to their potent ability to cause nephrotoxicity and ototoxicity, dosage limitations of Aminoglycosides pertain[9].

Gentamycin, an important aminoglycoside antibiotic, possess potent bactericidal activity for various Gram-negative microorganisms[10]. However, there are limitations to its use due to renal toxicity. Aminoglycoside-induced nephrotoxicity is confirmed by a rise in serum creatinine, serum urea and a marked decrease in glomerular filtration rate[11].

Drug-induced nephrotoxicity at renal tubular level more commonly affects proximal tubular cells due to high exposure to the drug and its metabolites during drug concentration and reabsorption through the glomerulus. Mitochondria are damaged in tubular cells, the tubular transport system is disturbed and there is increased oxidative stress due to the generation of free radicals leading to cell damage. Nephrotoxic drugs fiberize the kidney due to inflammation in glomerulus and proximal tubular cells and damage to surrounding renal cellular matrix[12].

The objective of the study was to determine the nephroprotective effect of ethanolic extract of *Carica papaya* seeds in Aminoglycoside induced acute nephrotoxicity.

Received on 14-05-2021
Accepted on 24-10-2021

METHODOLOGY

Through random selection using balloting method, rats were sub divided into three groups; I, II and III, with ten rats in each group. Group I was taken as a control group throughout the experiment. Group II and III (10 rats each) were given the Aminoglycoside drug gentamycin (80 mg/kg) via intraperitoneal route for five consecutive days for[11] induction of acute nephrotoxicity. serum urea, and serum creatinine were measured on day 6 to see that[13] nephrotoxicities were developed. After the confirmation of nephrotoxicity on day 6, Group III was started with the administration of Ethanolic Extract of *Carica papaya* seeds (1000 mg/kg) dissolved in[14] distilled water for five consecutive days. After terminal sampling through the cardiac puncture, serum urea and creatinine were measured again on Day 11 to see the effect of ethanolic extract of *Carica papaya* seeds on renal function. *Carica papaya* plants were grown locally. Seeds were air-dried after collection from ripened fruits. They were then identified and authenticated by the Herbarium Section of National Agricultural Research Centre (NARC) Islamabad. The air-dried seeds were pulverized and were immersed in ethanol (80%). The solution was put in a conical percolator for 72 hours. After 72 hours, it was filtered with a sieve of 80µm pore size filter paper. The filtrate was concentrated using a rotary evaporator. The extracts were then weighed and stored in sealed plastic containers at 40 C[15].

Statistical analysis: The data was analyzed using Microsoft Excel 2010 and SPSS 20. Multiple comparisons were made through

Tuckey test, and group mean differences were observed. A p-value of <0.05 was considered significant statistically.

RESULTS

Mean value of serum urea for Group I (Control Group) on Day 6 was 24.70 mg/dL 1.633. Mean values of serum urea for Group II (Disease Control Group) and Group III were 81.00 mg/dl ± 1.247 and 82.70 mg/dl ± 2.587. There was a significant difference (p-Value less than 0.05). This suggested induction of acute nephrotoxicity by the Aminoglycoside drug Gentamycin.

Mean serum urea for Group III (Ethanolic Extract Treated Group) at day 11 was 72.40 ± .991* after five days of treatment by ethanolic extract of *Carica papaya* seeds. There was a significant difference (p-Value <0.05) which supported the nephroprotection by the herb.

Mean value of serum creatinine on Day 6 for Group I (Control Group) was 0.750 mg/dL 0.0619. The mean values of serum creatinine for Group II (Disease Control Group) and Group III were 1.980 ± .0467 and 2.030 ± .0667. There was a significant difference (p-value .000). This suggested induction of nephrotoxicity by Aminoglycoside drug Gentamycin.

Mean serum Creatinine for Group III (Ethanolic Extract Treated Group) was 1.680 ± .0467 after five days of treatment by ethanolic extract of Carica papaya seeds. There was a significant difference (p-Value <0.05) which supported the nephroprotection by the herb.

Table-1: Mean Values of Serum Urea of All Groups at Day 0, 6 And 11

Serum Urea Groups	Day 0	Day 6	Day 11
Group I (control group	24.90 ± 1.633	24.70 ± 1.633	24.70 ± 1.633
Group II (Disease Control)	24.70 ± 1.760	81.00 ± 1.247***	78.60 ± 1.240
Group III(Ethanolic Extract)	23.40 ± 1.507	82.10 ± 1.233***	72.40 ± .991*
p-value	< .05	< 0.05	< 0.05

*Statistically significant

Table 2: Mean Values of Serum Creatinine of All Groups at Day 0, 6 And 11

Serum Creatinine Groups	Day 0	Day 6	Day 11
Group I (control group	.750 ± .0619	.750 ± .0619	.750 ± .0619
Group II (Disease Control)	.780 ± .0611	1.980 ± .0467***	1.920 ± .0389
Group III (Ethanolic Extract Treated Group)	.770 ± .0667	1.990 ± .0379***	1.680 ± .0467*
p-value	<.05	< .05	< 0.05

DISCUSSION

Xenobiotics are detoxified and eliminated by vital functions of kidneys making them vulnerable for acute damage[1]. Acute kidney injury (AKI) possesses high morbidity and mortality as a common complication. Gentamycin, an important Aminoglycoside antibiotic, has a potent antibiotic spectrum while the drug also cause acute nephrotoxicity which accounts for 10 to 15 % cases among the acute renal failure in drug induced kidney damage[10]. Due to its cost-effectiveness and high potency, and more liability to cause toxicity in kidneys, Gentamycin is widely used for inducing nephrotoxicity in experimental models[13].

Baseline serum urea and serum creatinine were measured at Day 0, i.e., beginning of the experiment. Gentamycin was administered intraperitoneally to Group II and Group III for five consecutive days. On day 6, Mean serum urea and serum creatinine were again measured. Mean serum urea and creatinine of Group II (Disease Control Group) and Group III were significantly raised compared with Control Group I, suggesting that Gentamycin produced acute nephrotoxic changes in the kidney and altered the renal function.

After measuring the serum markers, Group III was started by administering an ethanolic extract of *Carica papaya* seeds dissolved in distilled water via oral route. The ethanolic extract was administered for five consecutive days. On Day 11, again, serum markers were measured and the values of serum urea and serum creatinine were found to have been reduced than Day 6 in Group III, which received ethanolic extract of *Carica papaya* seeds.

There was a significant difference statistically between the Disease Control Group, i.e., Group II and the Ethanolic Extract treated group, Group III (p-Value less than 0.05). The difference in serum markers showed nephroprotection by ethanolic extract of *Carica papaya* seeds. Gentamycin resulted in increased serum markers, i.e. serum urea and creatinine in Group II and Group III after five days of intraperitoneal administration of the drug in a dose of 80 mg/kg compared to Group I, i.e., Control Group. These findings were found to be consistent with findings of a study by (Ajami M et al.; 2010), in which nephrotoxicity was induced in male Wister rats via Gentamycin in the same dose that resulted in increased levels of serum markers, i.e., serum urea and creatinine[13].

After the induction of nephrotoxicity, the protective effect of ethanolic extract of *Carica papaya* seeds was observed when 1000 mg/kg dose of ethanolic extract of *Carica papaya* seeds was administered to Group III. This was consistent with the study in which the same dose of Chloroform extract of *Carica papaya* seeds was utilized in rats for toxicity studies[16].

In the current study, ethanolic extract preparation of *Carica papaya* seeds was utilized, which revealed improved serum urea levels and serum creatinine in Group III after previous induction of nephrotoxicity by Gentamycin. The results indicated that Ethanolic extract of *Carica papaya* seeds could potentially prevent and reverse the renal damage in Gentamycin-induced acute nephrotoxicity.

Limitations: Our study had limitations like financial constraints and lack of resources. The cost of the experiment limited the study of phytochemical constituents of the extract preparation.

CONCLUSION

We concluded that ethanolic extract of *Carica papaya* seeds has significant nephroprotective effects on Aminoglycoside induced acute nephrotoxicity in rats.

Authors' Contribution: SA&MT: Conceptualized the study, analyzed the data, and formulated the initial draft, **AM&AH:** Contributed to the histomorphological evaluation, **SAK:** Contributed to the analysis of data and proofread the draft, **MT:** Contributed to data collection, **TL:** Contributed to the proofreading the manuscript for intellectual content.

Conflict of Interest: None to declare

Financial Disclosure: None

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