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ORIGINAL ARTICLE

Histopathological Impact of Carica Papaya Seed Extract in Rat Model of Gentamicin Nephrotoxicity

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ABSTRACT

Background: Kidneys are susceptible to many commonly used drugs, owing to their property of filtering, reabsorbing, and excreting multiple drugs.
Aim: To study the renoprotective effect of ethanolic seed extract of Carica papaya on renal histomorphology in nephrotoxicity caused by Gentamicin**.**
Study design: Experimental study.
Methodology: Rats (n=30) were subdivided into 3 equal groups. Group I (control group) and Group II & III were administered Gentamicin (80 mg/kg) was given daily for 05 days continuously, intra-peritoneally to cause nephro-toxicity. Histomorphological examination of kidney tissue was done on day-6. In group-III, ethanolic extract of Carica papaya seeds (1000 mg/kg) was given daily for 5 days orally for its induction of nephro-protective effects. Data was entered and analyzed in computer using SPSS.
Results: Acute Tubular Necrosis (ATN) and presence of Hyaline casts in the lumen of proximal tubules were the distinctive morphological characteristics. Histopathological specimens of the kidney in Ethanolic treated group showed moderate characteristics of renal damage as compared to that of the disease control group.
Conclusion: Study concluded that that Carica papaya seed extract can significantly ameliorate the nephrotoxic effects of Gentamicin thus nephro-protective.
Keywords: Gentamicin, Carica papaya, Nephrotoxicity and Histomorphology.

INTRODUCTION

Renal damage occurs usually on exposure to various drugs resulting in development of acute or chronic kidney failure[1]. Among hospitalized patients (6%) experience adverse drug reactions with majority were reported to be drug-associated toxicities[2].

Almost 25% cases of acute renal failure results from nephrotoxic drugs in terminally ill patients as revealed by many studies[3]. Kidneys are the major excretory organs of body thus they are susceptible to many commonly used drugs and their side effects. This occurs mainly due to their property of filtering, reabsorbing, and excreting multiple drugs. Drugs mainly include antibiotics, anti-cancers, anti-virals and immunosuppressant drugs, which have been termed as nephrotoxic[4].

Among all antibiotics, amino-glycosides are the major component of therapeutic regimens commonly given for the treatment of both gram-positive as well as gram-negative bacterial infections due to their cost-effectiveness and efficacy.[5] Their excretion mainly occurs through glomerular filtration in the urine in an unchanged form[6]. However, their dose limitations is a serious concern among physician due to their side effects that produce oto-toxicity and nephrotoxicity[7]. Gentamicin is a bactericidal drug for gram-negative bacteria, though, their use has decreased owing to its nephrotoxic potential[8].

According to previous studies that showed that most commonly affected part of the renal tubules is proximal tubular cells in drug-induced nephro-toxicity. This is mainly due to their characteristics like re-absorption and excretion of drugs and their metabolites at the glomerular level. Other mechanism includes increased oxidative stress as a result of free radicals that damages mitochondria and disrupts the tubular transport system. Damage to renal cellular matrix and fibrosis of surrounding tissue usually result from inflammatory processes of glomerular and proximal tubular cells[9]. Acute renal injury is characterized histologically by acute tubular necrosis (ATN) and hyaline casts in the proximal tubular lumen[10].

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Gentamicin produces Reactive Oxygen Species (ROS) that cause apoptosis, tubular necrosis and appearance of casts in tubular cells leading to cell death[11,12]. In various illnesses, *Carica papaya* because of its antioxidant and free radical scavenging properties have been employed but its nephro-protective effect is unrevealed hence current study was proposed.

The objective of the study was to study the reno-protective effect of ethanolic seed extract of Carica papaya on renal histomorphology in nephrotoxicity caused by Gentamicin**.**

METHODOLOGY

The study was conducted at "Department of Pharmacology and Therapeutics" and "Multidisciplinary Laboratory of Islamic International Medical College, Riphah International University" and National Institution of Health, Islamabad. Healthy 30 rats weighing 300-350 grams and normal renal function tests were included. They were divided into 3 groups with 10 rats in each group. Group I (control group) and Group II & III were administered Gentamicin (80 mg/kg) was given daily for 05 days continuously, intra-peritoneally to cause nephro-toxicity. Histomorphological examination of kidney tissue was done on day-6. In group-III, ethanolic extract of Carica papaya seeds (1000 mg/kg) was given daily for 5 days orally for its induction of nephro-protective effects. Rats weighing less than 300 grams and abnormal renal function tests were excluded.
Statistical Analysis: All data was analyzed through SPSS version 24.0. Results were described in terms of grades on histological basis.

RESULTS

Group-I (Control Group): Histopathological specimens of kidneys in this group showed normal appearance as in figure-1.
Group-II (Disease Control Group): Histopathological specimens of kidneys in this group showed severe renal injury. Acute Tubular Necrosis (ATN) and Hyaline casts in proximal tubular lumen were the distinctive morphological characteristics as shown in table-1 and figure-2.

Figure-1: Normal Cells of Renal Tissue at 40X

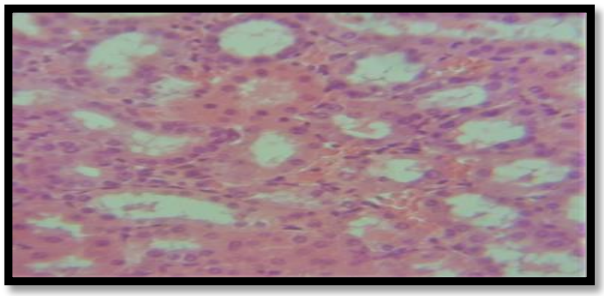
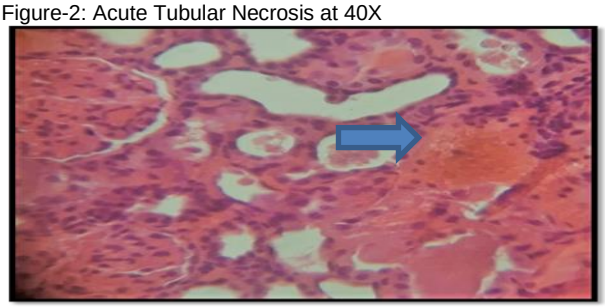
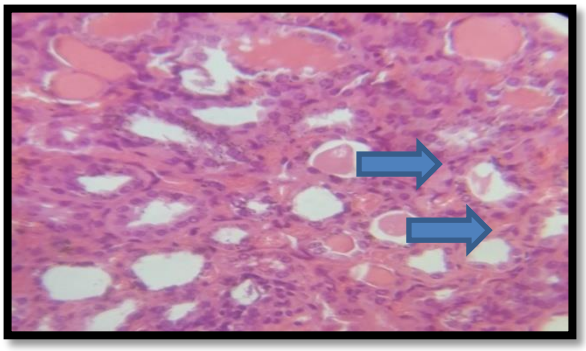


Figure-2: Acute Tubular Necrosis at 40X



Hyaline Casts in Lumen of Proximal Tubule:

Figure-3: Hyaline Casts in Tubular Lumen at 40X



Group-III (Ethanolic Extract Treated Group): Histopathological specimens of the kidney showed moderate characteristics of renal damage as compared to that of the disease control group. The aforementioned histological changes revealed that *Carica papaya* seed extract can significantly ameliorate the nephrotoxic effects of Gentamicin.

Table-1: Distribution of Acute Tubular Necrosis in Kidney

Experimental Groups	Acute Tubular Necrosis (N=30)					
	Absent	Mild	Moderate	Severe	Very Severe	Total
Group I (Control Group)	10	0	0	0	0	10
Group II (Disease Control Group)	0	2+	2 ++	5+++	1++++	10
Group III (Ethanolic Extract Group)	0	2+	3++	4+++	1++++	10
Total	10	4	5	9	2	30

*ATN GRADES: 0 = normal, + = mild, ++ = moderate, +++ = severe, ++++ = very severe

Table-2: Distribution of Hyaline Casts In Tubular Lumen

Experimental Groups	Hyaline Casts in Tubular Lumen					
	Absent	Mild	Moderate	Severe	Very Severe	Total
Group I (Control Group)	10	0	0	0	0	10
Group II (Disease Control Group)	0	1	2	4	3	10
Group III (Ethanolic Extract Group)	0	1	4	3	2	10
Total	10	2	6	7	5	30

*HC GRADES: 0 = normal, + = mild, ++ = moderate, +++ = severe, ++++ = very severe

DISCUSSION

Xenobiotics are detoxified and eliminated via the kidneys, rendering them vulnerable to acute injury. High morbidity and mortality rates are common complications of Acute Kidney Injury (AKI)[13,14,15]. Gentamicin, an essential Aminoglycoside antibiotic despite an effective antibiotic activity, causes acute nephrotoxicity as a complication. Owing to its affordability, potency, and nephrotoxic potential, Gentamicin is widely used in experimental models for nephrotoxicity induction[16].

Intraperitoneally administered Gentamicin (80mg/kg) produces nephrotoxicity by raising the serum markers and brings forth histomorphological changes like infiltration of inflammatory cells, hyaline casts in the tubular lumen, and proximal tubular necrosis in renal tissue.[17-21] Present study aimed at giving no treatment to group II with Gentamicin and the aforementioned changes were studied in the kidneys.

The morphological changes of nephrotoxicity displayed reversal in Group III, treated with ethanolic extract as compared to Group II (disease control group) which was only administered gentamicin. This improvement in histopathological parameters is in accordance with the study of Madinah et al. who also witnessed improvement in kidney architecture with pre-treatment with the herb[13]. In another study Francis et al. reversed signs of renal injury induced by mercuric chloride, including tubular necrosis and presence of hyaline casts, by using ethanolic extract of Carica papaya leaves at a dose of 300 mg/kg body wt. as well as 600mg/kg body wt[22].

A study conducted by Subal et al. evaluated the nephroprotective effect of ethanolic extract of *Carica papaya* seeds in mice and concluded that histopathological signs of renal damage were greatly improved upon treatment with the extract[23]. This result was consistent with the findings of our study where Group III showed significant improvement in proximal tubular necrosis and absence of hyaline casts when treated with the ethanolic extract of *Carica Papaya* seeds. The results showed that renal damage in Gentamicin induced nephrotoxicity can potentially be prevented and reversed by ethanolic seed extract of *Carica papaya.*

Limitations: Financial constraints, lack of resources and short duration of study were the limitations.

CONCLUSION

It was concluded that ethanolic extract of Carica Papaya had effective reno-protective activity. It was endorsed by reversal of histomorphological features of renal damage in a nephrotoxic rat model.

Authors' Contribution: SA&MT: Conceptualized the study, analyzed the data, and formulated the initial draft, **SAK&MAS:** Contributed to the proof reading, **AM,AH&TL:** Collected data.
Conflict of Interest: None to declare
Financial Disclosure: None

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