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# Nephroprotective Activity of Aqueous Extract of *Carica Papaya* Seeds in Carbon Tetrachloride Induced Nephrotoxic Rats

*Mst. Shahin Sultana,[1] Rekha Rani Saha,[2] Sheikh Nazrul Islam,[3] Tasnin Afrin,[4] Rumana Afroz,[5] Mahbuba Jahan Lotus[6]*

ORIGINAL ARTICLE


## ABSTRACT

***Background & objective:*** The kidney plays a dominant role in homeostasis by excreting the metabolic waste products and excess of necessary substances. It is a major excretory organ regulating water and electrolyte balance and conserving necessary products according to body needs. Nephrotoxicity is one of the most common kidney problems. A number of therapeutic agents can adversely affect the kidney resulting in acute renal failure, chronic interstitial nephritis and nephritic syndrome. Nephroprotective agents are the substances which possess protective activity against Nephrotoxicity. Early literatures have prescribed several herbal and medicinal plants, that are used as nephroprotective agents. Several herbal and medicinal plants are used as nephroprotective agents in experimental animals. *Carica papaya* was reported to have antioxidant and free radical scavenging activities. The present study was performed to determine the nephroprotective role of aqueous extract of *Carica papaya* seeds on carbon tetrachloride (CCl4) induced nephrotoxic rats.

***Methods:*** For the purpose of the study 28 healthy, male, wistar albino rats were taken and randomly divided into four groups (Group-A, Group-B, Group-C, and Group-D), each group formed of 7 rats. Group A received laboratory diet for 7 days. Group B received laboratory diet for 7 days. Group C and group D received aqueous extract of *Carica papaya* seeds (CPE) 250 mg/kg/day and 500 mg/kg/day respectively for 7 days. On 8$^{th}$ day a single intraperitoneal injection of 1.5 ml/kg of 20% CCl4 dissolved in olive oil was given to the rats of group B, group C and group D for induction of nephrotoxicity. All the animals were sacrificed on 11$^{th}$ day and their blood and kidney samples were collected. Serum creatinine, urea and uric acid were estimated and histopathology of kidney was done.

***Result:*** Result showed that the highest level of serum creatinine and urea were exhibited by the rats of Group-B and lowest level by the rats of Group-A. The levels of the same biochemical variables in Group-C and Group-D were in between the levels found in Group-A & Group-B ($p = 0.004$ and $p = 0.001$ respectively). The serum creatinine and urea levels remain normal and histopathological architecture was almost maintained in rats, treated with aqueous extract of *Carica papaya* seeds 500 mg/kg/day before nephrotoxicity induced in them by Carbon tetrachloride (CCl4) injection, although these biochemical values were elevated and histopathological structure was altered in rats, treated with Carbon tetrachloride (CCl4) injection and no CPE was given before (Group-B). The study also revealed that *Carica papaya* seeds 500 mg/kg/day was more protective than 250 mg/kg/day as was evidenced by lower serum urea level in the Group-D (31.73 ± 4.29 mg/dl) than that in Group-C (52.47 ± 5.38 mg/dl) ($p < 0.001$).

***Conclusion:*** The study concluded that *Carica papaya* seeds have nephroprotective activity against nephrotoxic effect of CCl4. Renal histological architecture was almost maintained by *Carica papaya*. Higher dose of *Carica papaya* provides better protection.


***Key words:*** Nephroprotective, aqueous extract, *Carica papaya*, Carbon tetrachloride (CCl4), Nephrotoxicity, rats etc.


***Authors' information:***

[1] ***Dr. Mst. Shahin Sultana,*** *Assistant professor, Department of Pharmacology, Dhaka Medical College, Bangladesh.*

[2] ***Prof. Dr. Rekha Rani Saha,*** *Ex Professor, Department of Pharmacology, Sir Salimullah Medical College, Bangladesh.*

[3] ***Prof. Sheikh Nazrul Islam,*** *Director & Professor, Institute of Nutrition and Food Science University of Dhaka, Bangladesh.*

[4] ***Dr. Tasnin Afrin,*** *Associate Professor, Department of Pharmacology, Mainamoti Medical College, Cumilla, Bangladesh.*

[5] ***Dr. Rumana Afroz,*** *Associate Professor, Department of Pharmacology, Dhaka Medical College, Bangladesh.*

[6] ***Dr. Mahbuba Jahan Lotus,*** *Assistant professor, Department of Pharmacology, Dhaka Medical College, Bangladesh.*

***Correspondence:*** ***Dr. Mst. Shahin Sultana,*** *Mobile: 01712151555, E-mail: shahinsultana4@gmail.com*

## INTRODUCTION:

The kidney is an essential organ of our body, which plays a dominant role in homeostasis by excreting the metabolic waste products and excess of necessary substances, regulating water and electrolyte balance and conserving necessary products according to body needs.[1] Kidneys are important regulators of blood pressure, glucose metabolism and erythropoiesis.[2] It is especially susceptible organ to toxic injuries and is the prime target of several drugs, toxic xenobiotics or chemicals because of its high blood supply (receives 20-25% of cardiac output) and presence of cellular transport systems that causes accumulation of these compounds within the nephron epithelial cells.[3]

Nephrotoxicity is one of the most common kidney problems and occurs when body is exposed to a drug or toxin.[4] A number of therapeutic agents (aminoglycoside antibiotics, NSAID's, chemotherapeutic agents) can adversely affect kidneys resulting in acute renal failure, chronic interstitial nephritis and nephritic syndrome.[5] Exposure to chemical reagents like ethylene glycol, carbon tetrachloride, sodium oxalate and heavy metals such as lead, mercury, cadmium and arsenic also induces nephrotoxicity.[6] Nephroprotective agents are the substances which possess protective activity against nephrotoxicity. Early literatures have prescribed various herbs for the cure of renal disorders.[7] Co-administration of various medicinal plants possessing nephroprotective activity along with different nephrotoxic agents may attenuate toxicity of the nephrotoxic agents.[8] Several herbal and medicinal plants are used as nephroprotective agents in experimental animals such as Nigella sativa,[9] Rhazya stricta[10] garlic,[11] Vitamin A and C,[12] green tea,[13] olive leaf,[14] Sida cordifolia.[15] It is assumed that natural agents may offer comparatively safer alternatives to other agents. The use of medicinal plants by people in developing countries is popular, for these products are safe, widely accessible at low cost.[16]

The *Carica papaya* (CP) is a member of the small family Caricaceae, commonly grown in Bangladesh, West Indies, Philippines, Sri Lanka, India, Malaysia and in other regions of tropical America. A lot of commercial products is prepared from different parts of *Carica papaya* plant, such as, fruit juice, seed oil which have medicinal value. The different parts of the plant (the fruits, leaves, latex and seeds) are also eaten for medicinal purposes.[17] The unripe fruit is used traditionally for the treatment of various human and veterinary diseases including malaria, hypertension, diabetes mellitus, hypercholesterolaemia, jaundice, intestinal helminthiasis[18] and for the management of sickle cell anaemia.[19] Scientific evidences have shown that *Carica papaya* has the following activities: anti-diabetic,[20-22] diuretic,[23] antihyperlipidemic,[24] antihelminthic, anti-amoebic,[25] bactericidal[26] nephroprotective,[22] anti-oxidant[27] etc. The present study was designed to investigate the effect of graded oral doses of the aqueous extract of mature unripe *Carica papaya* seed (CPE) in $CCl_4$ induced nephrotoxic rats as a way of validating this folkloric use with the hypothesis in mind that aqueous extract of *Carica papaya* seeds have nephroprotective effect in carbon tetrachloride ($CCl_4$) induced nephrotoxic rats.

## METHODS:

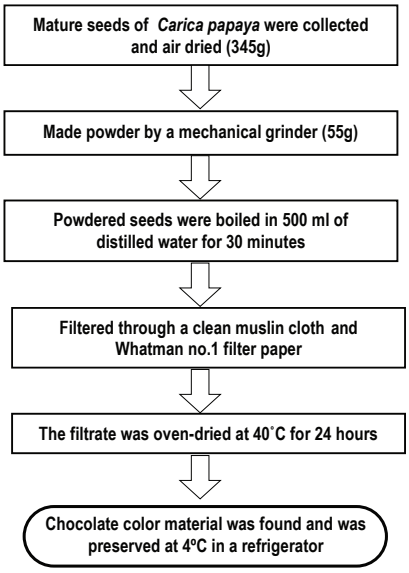
This Experimental study was conducted in the Department of Pharmacology and Therapeutics, Sir Salimumullah Medical College & Mitford Hospital (SSMC & MH), Dhaka over a period of 1 (one) year from July 2014 to June 2015. The experiment was performed on 28 healthy adult male wister albino rats (*Rattus norvegicus*) weighing between 120-180 gm, collected from ICDDRB, Dhaka. All animals were conditioned in standard metallic cages (single rat per cage), fed standard laboratory diet and allowed free access to drinking water. The animals were also kept in 12:12 hour light/dark cycle. After two weeks of adaptation, rats were randomly divided into four groups. The experimental rats were handled in strict compliance with international guidelines as prescribed by the Canadian Council on the Care and Use of Laboratory Animals in Biomedical Research in 1984.[28]

**Preparation of material (extract):**

Aqueous extract of *Carica papaya* seeds (CPE) was prepared in the laboratory of Institute of Nutrition and Food Science, Dhaka University. The method of extract preparation followed the method used by

Olagunju et al[29] in their experiment. Ten mature fruits of *Carica papaya* were collected from local market of Dhaka. Fruits identification and authentication were done by the Department of Botany, Dhaka University. The fruits were cut into pieces and the wet seeds were separated out. The weight of wet seeds was 345 gm. These were then gently but thoroughly rinsed in tap water for two times and completely air dried at room temperature for 2 weeks. The dried seeds were pulverized into fine powder using a new domestic mixer grinder. The weight of powdered *Carica papaya* seeds were 55 gm, which was then boiled in 500 ml of distilled water for 30 minutes, cooled at room temperature for 4 hours and was filtered through a clean muslin cloth. The filtrate was subsequently filtered through Whatman no.1 filter paper. The filtrate thus obtained was oven-dried at 40°C for 24 hours to obtain a semi-solid, chocolate color material. The chocolate color material, that obtained were pooled and stored in air-tight glass container and kept in a refrigerator at 4ºC. The diagram below is showing the preparation of *Carica papaya* extract.

**Preparation of aqueous extract of Carica papaya L. seeds**




**Experimental procedure:**

For determination of the dose-related protective effect of aqueous extract of *Carica papaya* seeds (CPE) 28 rats were taken and grouped as follows:

Two experimental groups of rats were separately treated with 250 mg/kg and 500 mg/kg of CPE for 7 days (day 1 to day 7) and two untreated groups were designated as normal control and model control. The dose of aqueous extract of *Carica papaya* L. seeds (CPE) was chosen based on the dose used in the research done by Alqasoumi[30] and duration of treatment was adopted from the research done by Olagunju et al.[29] In the present study nephrotoxicity was induced by Carbon tetrachloride ($CCl_4$). The dose and route of Carbon tetrachloride ($CCl_4$) was selected according to the experiment of Lu et al.[31] To conduct the study, 28 male, wistar albino rats were taken and randomly divided into four groups (Group-A, Group-B, Group-C, and Group-D) each group consisting of 7 rats. Accordingly, Group A & B received laboratory diet for 7 days. Group C & D along with laboratory diet received aqueous extract of *Carica papaya* seeds (CPE) 250 mg/kg/day and 500 mg/kg/day respectively for 7 days. On 8$^{th}$ day a single intraperitoneal injection of 1.5 ml/kg of 20% $CCl_4$ dissolved in olive oil was given to all the rats of group-B, group-C and group-D for induction of nephrotoxicity. All the animals were sacrificed on 11$^{th}$ day and their blood and kidney samples were collected. Serum creatinine, urea and uric acid were estimated and histopathology of kidney was done.

At the end of experimentation (72 hours after the $CCl_4$ injection), rats were sacrificed by cervical dislocation. Just before sacrifice, the animals were anesthetized with Chloroform. Approximately 2-3 ml of blood from each rat was collected by cardiac puncture and was put into a separate heparinized container with proper identification numbers. Serum, separated after centrifugation at 4000 rpm for 5 minutes, was collected with the help of micropipette and was transferred into separately labeled Eppendrof tubes and stored at -15°C for biochemical analysis.

Renal function parameters, such as, serum creatinine, urea and uric acid were done by an automated analyzer (Dimension R×L Max). Sampling, reagent delivery, mixing, processing and recording of results are automatically performed by the autoanalyzer. Serum creatinine was estimated by modified Jaffe's alkaline picrate method, serum urea

by enzymatic method (urease) and serum uric acid by modified uricase method. All biochemical tests were done in the Department of Biochemistry, BSMMU, Dhaka. Immediately after sacrificing the animals, kidneys were removed and washed thoroughly with 0.9% sodium chloride solution (normal saline) and were preserved in 10% formalin for subsequent histological processing (by Carlton method[32] in the Department of Pathology, SSMC, Dhaka. The gross histological features of kidney tissue sections were studied using an Olympus microscope for any evidence of abnormal changes. The gross histological changes were noted but no quantitative estimations were done.

**Statistical analysis of data:**

Data were analyzed using statistical software SPSS (Statistical Package for Social Sciences), version 22.0. One way analysis of variance (ANOVA) was used to test the variability among groups and multiple comparisons between different groups was made by Post-Hoc Hochberg test. The level of significance was set at 5% and p-value < 0.05 was considered significant.

## RESULTS:

Effect of aqueous extract of *Carica papaya* seeds on renal functions of $CCL_4$ induced nephrotoxic rats:

Table I shows the comparison of renal function parameters, such as, serum creatinine, serum urea and serum uric acid levels among the normal control (group-A), model control (group-B) & experimental groups (group-C and group-D) treated with aqueous extract of C. papaya seeds (CPE) and $CCl_4$. While the highest level of serum creatinine and urea were observed in Group-B (received laboratory diet+induced by $CCL_4$) and lowest level in Group-A (received laboratory diet alone), the levels of the same biochemical parameters in Group-C (received laboratory diet + CPE 250 mg/kg/day + induced by $CCL_4$) and Group-D (received laboratory diet + CPE 500 mg/kg/day + induced by $CCL_4$) were in between the levels found in Group-A and Group-B (p=0.004 and p = 0.001 respectively). The data indicate that despite Group-C and Group-D were induced by $CCL_4$, they were protected from having nephrotoxicity by CPE.

Carbon Tetrachloride ($CCl_4$) produced nephrotoxicity in group-B rats as evidenced by significantly higher serum creatinine level (0.60 ± 0.08 mg/dl) when compared with serum creatinine level of group-A (0.47 ± 0.05) (p = 0.004). The serum creatinine level in group-C was considerably lower (0.51 ± 0.07 mg/dl) than that in group-B (0.60 ± 0.08) (p = 0.06) indicating therapeutic action of CPE (250 mg/kg/day) on $CCl_4$ induced nephrotoxicity. CPE 500 mg/kg/day in group-D significantly reduced serum creatinine level (0.49 ± 0.04 mg/dl) as compared to serum creatinine levels in group-B (0.60 ± 0.08 mg/dl) and group-C (0.51 ± 0.07 mg/dl) (p = 0.006) (Table II).

Carbon Tetrachloride ($CCl_4$) induced nephrotoxicity in group-B rats, as indicated by significantly higher serum urea level (59.07 ± 7.04 mg/dl) compared to that in group-A (32.59 ± 3.08 mg/dl) (p < 0.001). The serum urea level in group-C was much reduced (52.47 ± 5.38 mg/dl) than that in group-B (59.07±7.04), although the difference between the two groups was not statistically significant (p=0.072). The group-D demonstrated significant reduction of serum urea level (31.73 ± 4.29 mg/dl) when compared to serum urea levels of group-B (59.07 ± 7.04 mg/dl) and group-C (52.47 ± 5.38 mg/dl) (p<0.001 and p < 0.001 respectively) (Table III).

Carbon Tetrachloride ($CCl_4$) did not produce any demonstrated changes in serum uric acid level in group-B (1.96 ± 0.47 mg/dl) compared with group-A (1.83 ± 0.44 mg/dl) (p = 0.609). CPE at a dose of 250 mg/kg/day (in group-C) had a little effect on serum uric acid level (1.86 ± 0.40 mg/dl) as compared with group B (1.96 ± 0.47 mg/dl) (p=0.678). CPE at a dose of 500 mg/kg/day (in group D) also did not produce any commendable change in serum uric acid level (1.73 ± 0.28 mg/dl) in comparison to group-B (1.96 ± 0.47 mg/dl) (p=0.293) (Table IV).

**Table I. Effect of aqueous extract of *Carica papaya* seeds on kidney function in $CCL_4$ induced nephrotoxic rats:**

| Renal function parameters (mg/dl) | Group | | | | *p-value |
|---|---|---|---|---|---|
| | Group A | Group A | Group A | Group A | |
| Serum creatinine | 0.47 ± 0.05 | 0.60 ± 0.08 | 0.51 ± 0.07 | 0.49 ± 0.04 | F=0.57, p= 0.004 |
| Serum urea | 32.59 ± 3.08 | 59.07 ± 7.04 | 52.47 ± 5.38 | 31.73 ± 4.29 | F=2.48, p <0.001 |
| Serum uric acid | 1.83 ± 0.44 | 1.96 ± 0.47 | 1.86 ± 0.40 | 1.73 ± 0.28 | F=0.001 p = 0.61 |

Data were analyzed using **ANOVA statistics (F)** and were expressed as **mean ± SD.**
**Group A** (Normal control): Receive normal diet
**Group B** (Model control): Receive normal diet + Intraperitoneal $CCL_4$ after 7 days
**Group C** (Experimental 1): Receive normal diet + 250 mg/kg of CPE+ Intraperitoneal $CCL_4$ after 7 days
**Group D** (Experimental 2): Receive normal diet + 500 mg/kg of CPE+ Intraperitoneal $CCL_4$ after 7 days

**Table II. Multiple comparison of serum creatinine by Post-hoc Hochberg test**

| Group | Level of significance (p) |
|---|---|
| Group A vs. Group B | 0.004[s] |
| Group A vs. Group C | 0.205 |
| Group A vs. Group D | 0.552 |
| Group B vs. Group C | 0.060 |
| Group B vs. Group D | 0.006[s] |
| Group C vs. Group D | 0.356 |

S = Significant

**Table III. Multiple comparison of serum urea by Post-hoc Hochberg test**

| Group | Level of significance (p) |
|---|---|
| Group A vs. Group B | < 0.001[s] |
| Group A vs. Group C | < 0.001[s] |
| Group A vs. Group D | 0.675 |
| Group B vs. Group C | 0.072 |
| Group B vs. Group D | < 0.001[s] |
| Group C vs. Group D | < 0.001[s] |

S = Significant

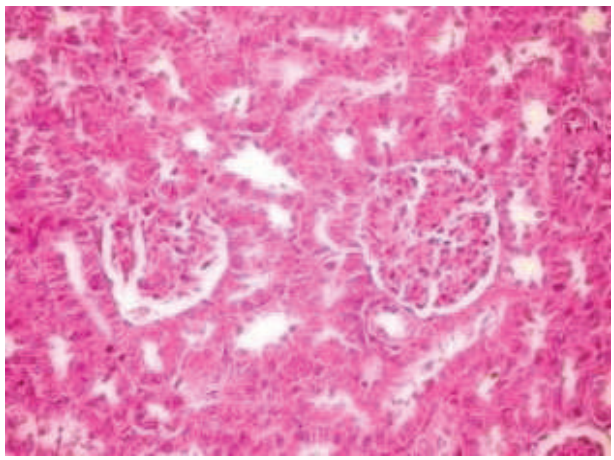
**Table IV. Multiple comparison of serum uric acid by Post-hoc Hochberg test**

| Group | Level of significance (p) |
|---|---|
| Group A vs. Group B | 0.609 |
| Group A vs. Group C | 0.902 |
| Group A vs. Group D | 0.623 |
| Group B vs. Group C | 0.678 |
| Group B vs. Group D | 0.293 |
| Group C vs. Group D | 0.502 |

### Histological observations:

The following histological changes were observed:

- Microscopic examination of sections from kidney of normal control group (Group-A, Photomicrograph I) treated with laboratory diet showing normal renal histological architecture of glomeruli, tubules and interstitium. The proximal tubular epithelium was lined by cuboidal cells with intact brush border.
- Microscopic examination of sections from kidney of model control group (group-B, Photomicrograph II) treated with laboratory diet for 7 days and intraperitoneal injection of $CCl_4$. On 8th day alleviation of renal architecture was evident showing vacuolations of endothelial lining of glomerular tufts as well as epithelial lining of renal tubules.
- Microscopic examination of sections from kidney of Experimental group 1 rat (Group C, Photomicrograph III) treated with laboratory diet and aqueous extract of *Carica papaya* L. seeds (CPE) 250 mg/kg/day for 7 days and intraperitoneal injection of $CCl_4$. On 8th day showing less vacuolation of endothelial lining of glomerular tufts as well as epithelial lining of renal tubules.
- Microscopic examination of sections from kidney of Experimental group 2 rat (group-D, Photomicrograph IV) treated with laboratory diet and aqueous extract of *Carica papaya* L. seeds (CPE) 500 mg/kg/day for 7 days and intraperitoneal injection of $CCl_4$. On 8th day, the slide shows almost normal renal histological architecture and there was very few vacuolation of epithelial lining of some renal tubules.



**Photomicrograph I : Section of kidney of group-A rat**

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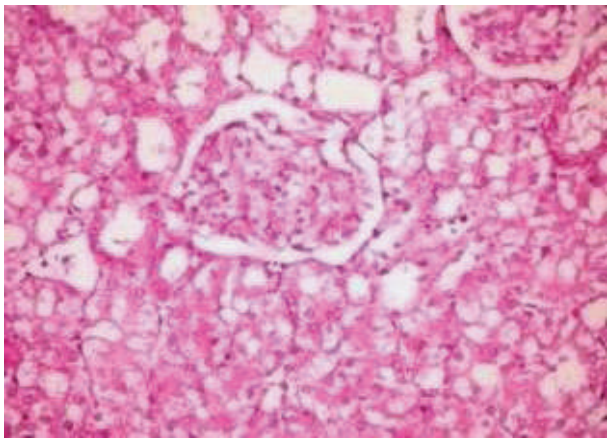
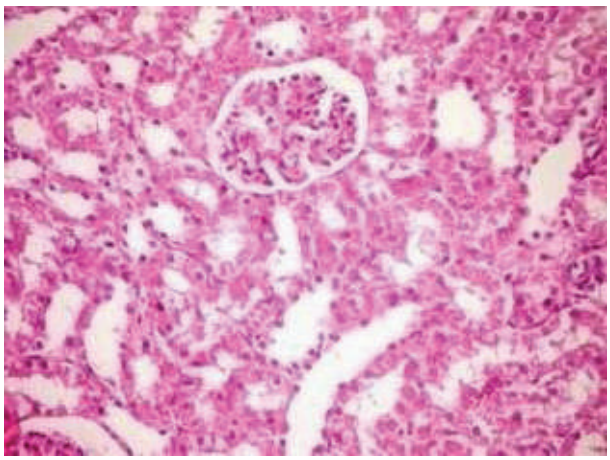
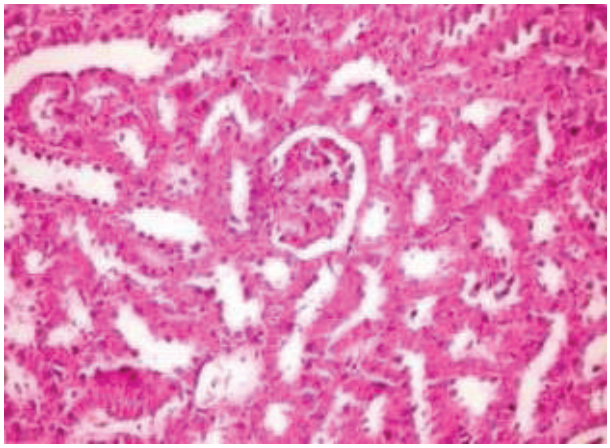


**Photomicrograph II : Section of kidney of group-B rat**



**Photomicrograph III : Section of kidney of group-C rat**



**Photomicrograph IV : Section of kidney of group D rat**

## DISCUSSION:

The present study was intended to demonstrate the nephprotective effect of aqueous extract of mature *Carica papaya* seeds on carbon tetrachloride induced nephrotoxic rats. As a measure of renal function status, serum creatinine and urea are often regarded as reliable markers.[33] Thus, elevations in the serum concentrations of these markers are indicative of renal injury.[33] In this study serum creatinine, urea, uric acid and kidney histopathology were used as kidney function parameters as they were used by Olagunju et al[29] In the present study nephrotoxicity was induced by Carbon Tetrachloride ($CCl_4$). A single dose of intraperitoneal (i/p) injection of Carbon Tetrachloride ($CCl_4$) (1.5 ml/kg of 20% CCl4 dissolved in olive oil) was given to cause nephrotoxicity. Carbon Tetrachloride is known to undergo reductive metabolism into a highly reactive Trichloromethyl radical ($CCl_3$) and phosgene, that initiates lipid peroxidation, disrupts membrane integrity and causes cell death.[34,35] After 72 hours of $CCl_4$ administration blood sample was collected for biochemical tests. The dose and route of $CCl_4$ was selected according to the experiment of Lu et al.[1]

In group-B after $CCl_4$ administration, serum creatinine and serum urea levels were significantly increased compared to normal control group. The level of serum uric acid was also increased but it was found insignificant. Similar observation was reported by Olagunju et al[29] and Venkatanarayana et al[36] in their experiment. Olagunju[29] however, showed that all the kidney function parameters (serum creatinine, serum urea and serum uric acid) levels were increased significantly after a single dose of $CCl_4$ injection.

Aqueous CPE 250 mg/kg/day considerably reduced serum creatinine and urea levels as compared to group-B. But it had little effect on serum uric acid level. Similar observation was made by Olagunju et al[29] in his experiment. They investigated the nephroprotective activity of aqueous CPE seeds in Carbon tetrachloride ($CCL_4$) induced nephrotoxic rats. Their study showed that 200 mg/kg/day of aqueous CPE seeds did not reduce serum creatinine level significantly but the same dose significantly reduced serum urea and uric acid levels. The aqueous CPE seeds in doses of 500 mg/kg/day significantly reduced serum creatinine and urea levels compared to group-B and group-C. But the same dose of CPE had negligible effect on serum uric

acid level. Olagunju et al[29] in their study showed that 400 mg/kg/day of CPE had significant effect in the reduction of serum creatinine, urea and uric acid levels.

Additionally, histopathological study of kidney demonstrated that treatment with $CCl_4$ causes alleviation of renal architecture with vacuolization of endothelial lining of glomerular tufts as well as epithelial lining of renal tubules (Photomicrograph II). Similar observation was reported by Venkatanaryana et al[36] in their study. He investigated the protective effect of Curcumin and Vitamin E on Carbon Tetrachloride ($CCl_4$) induced nephrotoxicity in rats. Administration of $CCl_4$ caused nephrotoxicity as indicated by elevation of urine and serum levels of urea, creatinine and urobilinogen and decrease in creatinine clearance. Histopathological examination also revealed the degenerative changes in glomerulus, renal tubules and vacuolization of cells. Thus, the present study clearly showed that treatment with aqueous CPE for 7 days conferred nephroprotection on the $CCl_4$ induced nephrotoxicity in rats in a dose-dependent fashion. While CPE 250 mg/kg/day offered little protection with less vacuolization of endothelial lining of glomerular tufts and epithelial lining of renal tubules (Photomicrograph III), CPE 500 mg/kg/day offered maximum protection with almost normal renal histological architecture and very few vacuolization of epithelial lining of some renal tubules (Photomicrograph IV). Similar observation was reported by Olagunju et al[29] in their study with maximum protection being found from CPE at 400 mg/kg/day of oral dose.

Although, the possible mechanisms by which CPE offer protection against $CCl_4$ induced nephrotoxicity was not studied in the current study, it is possible that the protective effect of the extract is mediated through antioxidant and/or free-radical scavenging activities. Literature has shown medicinal plants with nephroprotective properties mediate their protection via antioxidant and/or free-radical scavenging activities due to the high concentration of flavonoids and alkaloids they contain.[37,38] Equally, saponins have been reported to protect liver and kidneys against carbon tetrachloride intoxication.[39] In addition, aqueous CPE has been reported to contain flavonoids, alkaloids, saponins and other active phytocomponents.[18] Summarizing the findings of the present study and the findings of similar studies presented so far, it is plausible for the alkaloid, flavonoid and saponin components of aqueous CPE to be responsible for the observed biological effects and could constitute areas of future research. Again, the nephroprotection offered by the extract could be due to the presence of any of the phyto-principles contained in it.

## CONCLUSION:

The study concluded that *Carica papaya* seeds have nephroprotective activity against nephrotoxic effect of $CCl_4$. *Carica papaya* administered in $CCl_4$ induced nephrotoxic rats help maintaining almost normal levels of serum creatinine and urea suggesting that it has nephroprotective role against $CCl_4$-provoked nephrotoxicity. Renal histological architecture of study rats was almost maintained by aqueous extract of *Carica papaya* seeds. Higher dose (500 mg/kg/day) of *Carica papaya* provides better protection.

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