

## Original Article

# Comparative Efficacy of Dried Fruits of *Carica Papaya* Linn. and Vitamin-E on Preventing Hepatotoxicity in Rats

MZ Sadeque<sup>1</sup>, ZA Begum<sup>2</sup>, BU Umar<sup>3</sup>, AH Ferdous<sup>4</sup>, S Sultana<sup>5</sup>, MK Uddin<sup>6</sup>,

### Abstract

In the absence of an effective treatment in modern medicine, efforts are being made to find suitable herbal remedies for hepatitis. This prospective experimental study was conducted in the department of Pharmacology and Therapeutics, Dhaka Medical College, Dhaka from July 2006 to June 2007 to evaluate the hepatoprotective effects of *Carica papaya* against carbon tetrachloride (CCl<sub>4</sub>) induced hepatotoxicity and compared it with that of vitamin-E. Total 36 adult rats were used and they were divided into six equal groups namely A, B, C, D, E and F. All the rats were fed with normal diet and 2ml distilled water orally for 7 days. In addition, Group D received *Carica papaya* extract, Group E received olive oil and Group F received vitamin E orally per day for 7 days. On the seventh day CCl<sub>4</sub> was administered to all the rats except Group A and was sacrificed on 8th day of experiment. Serum bilirubin, alanine amino transferase (ALT), aspartate amino transferase (AST), alkaline phosphatase and hepatic histopathology were done thereafter. *Carica papaya* and vitamin E showed significant hepatoprotection against CCl<sub>4</sub> induced hepatotoxicity but *Carica papaya* showed more significant changes in ALP level than vitamin E. Prevention of hepatic necrosis and fatty degeneration were also observed in *Carica papaya* and vitamin E pretreated rats but there is no significant difference.

**Key words:** *Carica papaya*, hepatoprotective effect, CCl<sub>4</sub>

### Introduction :

*Carica papaya* is a short, fast growing woody large herb to 10 or 12 feet in height. The green fruit contains papain similar to pepsin, pulp of the fresh fruit contain a soft yellow resin, fat, albiminoid sugar and pectin. Leaves contain an alkaloid called carpaine and a glucoside named carposide<sup>1</sup>. Fruits, latex and juice of *Carica papaya* are digestive and are used in dyspepsia, intestinal irritation, habitual constipation, chronic

diarrhea, bleeding piles and enlarged spleen and liver. The latex has anthelmintic and anti-inflammatory properties and is applied externally to speed the healing of wounds, ulcers, boils, warts and cancerous tumors<sup>2</sup>.

Apart from viral infections many of the commonly used drugs and chemicals are responsible for various types of liver disorders. About 10 to 20% of patients with fulminant hepatic failure have drug induced hepatotoxicity<sup>3</sup>. Viral hepatitis has become a menace to public health in Asia and Africa, making development of inexpensive control measures urgent<sup>4</sup>. Virus related liver diseases are important cause of morbidity and mortality in Bangladesh<sup>5</sup>.

In the absence of an effective treatment in modern medicine, efforts are being made to find suitable herbal drugs<sup>6</sup>. In previous work, the hepatoprotective activity of *Moringa oleifera*<sup>7</sup>, *Casaria ecsulenta*<sup>8</sup> and *Andrographis paniculata*<sup>9</sup> against paracetamol induced hepatotoxicity had been found. Some previous studies in India<sup>6</sup> and Africa<sup>10</sup> revealed hepatoprotective activity of *Carica papaya*. Several scientific papers are available regarding hepatoprotective effects of various types of medicinal plants but that of *Carica papaya* are yet to be evaluated in Bangladesh.

1. Dr. Md. Zafar Sadeque, MBBS, MPhil, Assistant Professor, Dept. of Pharmacology, Tairunnessa Memorial Medical College, Gazipur.
2. Prof. Dr. Zinnat Ara Begum, MBBS, MPhil, Professor, Centre of Medical Education, Mohakhali, Dhaka.
3. Dr. Badar Uddin Umar, MBBS, MPhil, Assistant Professor & Head, Dept. of Pharmacology, FMC, Faridpur.
4. Prof. Dr. Abul Hasnat Ferdous, MBBS, MSc. (UK), Professor & Head, Dept of Pharmacology, Dinajpur Medical College, Dinajpur.
5. Prof. Dr. Syeeda Sultana, MBBS, MPhil, Professor, Dept. of Pharmacology, NICVD, Sher-e-Bangla Nagar, Dhaka.
6. Dr. Md. Kamal Uddin, MBBS, MPhil, Assistant Professor & Head, Dept. of Pharmacology, Khulna Medical College, Khulna.
7. Dr. S. M. Md. Mahid-AI-Hasan, MBBS, M Phil, Assistant Professor, Green Life Medical College, Dhaka.

### Address of correspondence

Dr. Badar Uddin Umar, MBBS, MPhil, Assistant Professor & Head, Dept. of Pharmacology, FMC, Faridpur. Mobile: +88-01711703295. Email: badarkeka@yahoo.com

Vitamin E is a potent antioxidant, particularly with respect to lipid peroxidation, Fariss et al<sup>11</sup> in their study showed that vitamin E significantly reduced serum transaminases. Present study was chosen to evaluate the protective effects of dried fruits of *Carica papaya* Linn against carbon tetrachloride induced hepatotoxicity and compare it with that of vitamin E.

### Materials and Methods :

The fruits of *Carica papaya* were brought from a local market in Dhaka city. The preparation of the aqueous extract was performed in the Department of Chemistry of Dhaka University. The green fruits of *Carica papaya* were cut into small pieces, shade dried and powdered. To prepare aqueous extract, 200gms of powdered fruits of papaya were taken and mixed with 1500 ml of distilled water in a conical flask and kept for 24 hours with occasional shaking and stirring. Then filtration through fine cloth and kept for further 24 hours followed by refiltration by vacuum pump. Then the whole extract was concentrated with rotary vacuum evaporator under low temperature. Then the extract was put into freeze dryer to make it powder. Finally the extract was stored in refrigerator.

Thirty six healthy *Rattans norvigicus* rats of both sexes 8 to 10 weeks old weighing between 140 to 180 gm were procured from the animal house of International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B), Dhaka. The rats were well accommodated in metallic cages, at room temperature, in the animal house of Dhaka Medical College which was maintained in properly hygienic condition and well ventilated. The rats were fed with pelleted food (10 to 15 gm/rat/day), procured from the ICDDR, B animal house.

The rats were divided into six groups (Group A, Group B, Group C, Group D, Group E, and Group F), each group comprising of 6 rats, treated for 7 days and sacrificed on 8th day. For convenience, the experiment was divided into two parts: Experiment- I and Experiment-II. **Experiment- I** was designed to demonstrate the hepatotoxic effects of CCl<sub>4</sub> on normal rats. The rats of Group A and Group B were fed with normal diet and 2ml distilled water orally for 7 days. Group B was given CCl<sub>4</sub> at the dose of 1.25ml/kg/day orally on 7th day and sacrificed on 8th day of experiment.

**In Experiment-II** Group C received normal diet; 2ml distilled water per day orally for 7days. Group D received normal diet; 250mg/kg aqueous extract of

*Carica papaya* in a 2ml of water per day orally for 7 days. Group E (Control for vitamin-E) received normal diet, 1ml of olive oil per day orally for 7 days. Group F received normal diet, 250mg/kg vitamin E in 1ml of olive oil per day orally for 7 days. On the seventh day CCl<sub>4</sub> was administered to all the rats of experiment-II and were sacrificed on 8th day of experiment. On average, 3ml blood from each rat was collected by cardiac puncture done by a syringe piercing through the body wall for estimation of serum bilirubin, ALT, AST, and ALP levels of the rats. Livers were also collected to see the histological changes and to see the effects on liver weight variation.

### Results :

Experiment-I resulted in elevated level of biochemical parameters in CCl<sub>4</sub> treated group indicating the hepatotoxic effects of carbon tetrachloride (Table-I).

**Table-I:** Effects of CCl<sub>4</sub> on rats mean serum bilirubin, ALT, AST and ALP levels.

Groups	Serum bilirubin (mg/dl)	Serum ALT (u/l)	Serum AST (u/l)	Serum ALP (u/l)
Group A Normal control	0.53 ± 0.60	40.33 ± 3.66	54 ± 2.68	276 ± 27.03
Group B CCl <sub>4</sub> treated	0.72 ± 0.04*	525 ± 35.74***	265 ± 6.19***	425 ± 15***

N=6 rats in each group, NS = not significant, \* P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001 when compared to control group. Values are expressed as Mean ± SE.

In Experiment-II, the decrease in mean serum bilirubin level in the aqueous extract of *Carica papaya* pretreated group was not significant when compared to control. But the decrease in mean serum ALT and ALP levels were highly significant (p<0.001). Mean serum AST level was reduced less effectively though it was statistically significant (p<0.01). In vitamin E pretreated group the mean serum bilirubin level was unchanged in comparison to control group. But mean serum ALT and AST levels were decreased very significantly (p<0.001). Mean serum ALP level decreased less significantly (p<0.05) in comparison with the control group. The aqueous extract of *Carica papaya* and vitamin E showed significant hepatoprotection against CCl<sub>4</sub> induced hepatotoxicity but the aqueous extract of *Carica papaya* showed more significant changes in ALP level than vitamin E (Table-II).

**Table-II:** Effects of pretreatment with *Carica papaya* and vitamin E on mean serum bilirubin, ALT, AST and ALP levels in CCl<sub>4</sub> treated rats.

Groups	Serum bilirubin (mg/dl)	Serum ALT (u/l)	Serum AST (u/l)	Serum ALP (u/l)
Group C (Control)	0.70 ± 0.04	530 ± 34.92	260 ± 10.32	426.66 ± 19.08
Group D (Aqueous extract of <i>C. papaya</i> )	0.63 ± 0.03 <sup>NS</sup>	194.33 ± 12.86 <sup>***</sup>	203.33 ± 9.54 <sup>**</sup>	295.33 ± 15.67 <sup>***</sup>
Group E (Olive oil)	0.80 ± 0.05	528 ± 28.43	257 ± 7.16	422 ± 14.38
Group F (Vit-E)	0.80 ± 0.07 <sup>NS</sup>	186.66 ± 22.90 <sup>***</sup>	110 ± 6.43 <sup>***</sup>	333 ± 24.58*

N=6 rats in each group, NS = not significant, \* P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001 when compared to control group. Values are expressed as Mean ± SE.

Histological examination of the liver sections treated with carbon tetrachloride showed necrosis and fatty degeneration. When compared with control the histopathological changes of liver showed prevention of necrosis and fatty degeneration in *Carica papaya* and vitamin E pretreated rats. But changes among these two groups were not statistically significant.

### Discussion :

In the present work, hepatotoxicity was induced in experimental rats by administration of 1.25 ml/kg CCl<sub>4</sub> as single dose on 7th day. The hepatotoxicity was evidenced by a significant increase (p<0.001) in serum ALT, AST, and ALP levels of the experimental rats. In hepatotoxicity, the most important mechanism of cell injury by carbon tetrachloride involves the formation of reactive free radicals and subsequent lipid peroxidation. The free radicals produced locally cause auto oxidation of the polyenoic fatty acids present within the membrane phospholipids. There oxidative decomposition of the lipid is initiated and organic peroxides are formed after reacting with oxygen<sup>12</sup>. The lipid peroxidative degradation of biomembranes induced by carbon tetrachloride causes hepatotoxicity which is evidenced by an elevation in the serum marker enzymes namely AST, ALT, ALP and total bilirubin. Similar observations were made by a number of workers. Raj Kapoor et al<sup>6</sup>, Bardhan et al<sup>13</sup> and Al-Qarawi et al<sup>4</sup> demonstrated hepatotoxicity in experimental rats by administering carbon tetrachloride. They showed that carbon tetrachloride increased serum bilirubin, ALT, AST and ALP levels of the experimental rats.

In this study, the aqueous extract of *Carica papaya*

decreased the carbon tetrachloride induced elevated levels of the enzymes like serum ALT, AST and ALP which were statistically significant (p<0.001, p<0.01, p<0.001) compared to control group. Changes in ALT levels were similar for aqueous extract of *Carica papaya* and vitamin E but changes in ALP levels were more significant for aqueous extract of *Carica papaya* than that of vitamin E. The rats pretreated with extract of *Carica papaya* showed sign of hepatoprotection against carbon tetrachloride. Raj Kapoor et al<sup>6</sup> in their experiment showed a significant reduction in serum ALT, AST, ALP, total bilirubin and gamma glutamate transpeptidase (GGTP) levels in the groups treated with aqueous extract of *Carica papaya*. The enzyme levels were almost restored to normal. The finding of their study is in agreement with the present study although they have demonstrated a more complete recovery.

Histological slides of the carbon tetrachloride treated control rats' liver showed distortion of the hepatic architecture. The hepatocytes in the hepatic lobule showed hydropic changes, microvesicular steatosis and diffuse hepatocyte necrosis. Infiltration of small number of inflammatory cells was also found. Aqueous extract of *Carica papaya* and vitamin E pretreated rats liver showed retaining of hepatic architecture, but there was hydropic changes and microvesicular steatosis. There was no infiltration of inflammatory cells. Focal hepatocyte necrosis was found.

### Conclusion:

The objective of the present study was to evaluate the comparative hepatoprotective effect of *Carica papaya* and vitamin E on carbon tetrachloride induced hepatotoxicity in experimental rats. The results and observations of this study demonstrated hepatoprotection. However, further studies should be carried out to determine the active principles responsible for the hepatoprotective effects and its cellular mechanism of action. Toxicological studies of *Carica papaya* in animals should also be carried out before any clinical trial for suitability of using in man.

### References :

1. Samson JA. "Tropical Fruits" 2nd ed. New York: Longman scientific and technical publication; 1986. p.256-69.
2. Ghani A. Medicinal Plants of Bangladesh. 2nd ed. Dhaka: Asiatic Society of Bangladesh; 2003.p.1- 149.
3. Kaplowitz N, Simon FR, Stolz A. Drug induced hepatotoxicity. Ann. Int. Med. 1986; 104:826-39.
4. Al-Qarawi AA, Abdel-Rahman HA, El-Mougy SA. Hepatoprotective activity of *Licorice* in rat liver model. Journal of herbs, Spices and Medicinal plants. 2001; 8(1): 7-14.

5. Ahmed FS. Prevalence of transfusion transmitted viruses (HBV, HCV, and HIV) among multitransfused thalassamic children. (MD Thesis), BSMMU, Dhaka, 2005.
6. Raj Kapoor B, Jayakar B, Kavimani S, Muruges N. Effect of dried fruits of *Carica papaya* Linn on hepatotoxicity. Biol. Pharm. Bull. 2002; 25(12):1645-6.
7. Ruckmani K, Kavimani S, Anandan R, Jayakar B. Effect of *Moringa Oleifera* Lam on paracetamol induced hepatotoxicity. Indian J. Pharm. Sci. 1998; 60(1):33-5.
8. Jayakar B, Dubes R, Kavimani S. Effects of various extracts of *Casaria esculenta* on paracetamol induced hepatotoxicity. Indian Drugs 1999; 36(4):264-5.
9. Eva EO. Comparative hepatoprotective effects of *Andrographis paniculata* and alpha-tocopherol in paracetamol induced liver damage in rats (M Phil thesis), Dhaka: Dhaka Medical College, 2004.
10. Adeneye AA, Olagunju JA, Banjo AAF, Abdul SF, Sanusi OA, Sanni OO, Osarodion BA, Shonoiki OE. The Aqueous Seed Extract of *Carica papaya* Linn. Prevents Carbon Tetrachloride Induced Hepatotoxicity in Rats. International J of Appl Res in Nat Products. 2009; 2(2):19-32.
11. Fariss MW, Bryson KF, Hylton EE, Lippman HR, Stubin CH, Zhau XZ. Study of protection against carbon tetrachloride induced hepatotoxicity by pretreating rats with the hemisuccinate esters of tocopherol and cholesterol. Environ Health Perspect 1993; 101(6): 528-36.
12. Kumar V, Cotran RS and Robbins SL. Cell Injury and Adaptation. In: Vinay Kumar, Ramzi S. Cotran, Stanley L. Robbins. editors. Basic Pathology. 5th ed. India: Prism Books (PVT) LTD; 1992. p 1-24.
13. Bardhan P, Sharma SK, Gark NK. In vitro effect of an ayurvedic liver remedy on hepatic enzymes in carbon tetrachloride treated rats. Indian Journal of Medical Research. 1985; 82: 359.