Advances in Life Sciences 2012, 2(4): 124-127
DOI: 10.5923/j.als.20120204.08

Dose-dependent Attenuating Effects of Aqueous Extract of *Carica papaya* Seed on CarbonTetrachloride-Induced Renal Toxicity in Rats

Eze Kingsley Nwangwa

Department of Physiology, Facultyof Basic Medical Sciences, College of Health Sciences, Delta State University, P.M.B. 001, Abraka.Delta State. Nigeria

Abstract A reasonable population of the world today uses herbal drugs.Carica papaya is one of those fruits that is documented to have the potentials of being used for medicinal purposes.In the present study, theeffects of aqueous extract of Carica papaya seeds on a CCl4-induced renal toxicity was studied. A total of thirty (30) Wistar rats were randomly divided into five groups (n=6). Group 1 (control)was administered with rat chow and water. Group 2,3,4 and 5 received CCl4intraperitoneally (IP) at a dose of 0.8mg/kg and group 3, 4 and 5 received in addition 100mg/kg, 200mg/kg and 300mg/kg extract of Carica papayafor 28 days orally respectively. Samples were collected and assayed for the renal function markers (urea, creatinine and electrolyte). Results obtained showed a dose-dependent statistically-significant decrease in therenal function markers except potassium, which suggests that the extract has a nephro-protective effect. These findings need be further investigated for application in the health care delivery.

Keywords Carbontetrachloride, Nephro-Toxicity, *Carica Papaya*, Renal Function Markers, Free Radical Scavengers

1. Introduction

In the long history of the world, plants have been used medically. A large and increasing number of patients use medicinal herbs or seek the advice of their physician regarding their use[1]. It has been estimated roughly, that presently more than half of the total population of the world use herbal drugs[2]. Attention has been given to some tropical fruits that are of economic importance[3] amongwh ich *Carica papaya* (pawpaw) is one.

The *Carica papaya* (CP) is a member of the small family Caricaceae commonly grown in West Indies, Philippines,Sr i Lanka, India, Bangladesh, Malaysia and othercountries in tropical America. There are a lot ofcommercial products prepared from different parts of *Carica papaya*plant such as fruit juice, seed oil and supplement forhealth. The different parts of the plant (the fruits, leaves, latex and seeds) can be eaten and also havebeen used for medicinal purposes as claimed traditionallyfor treatment of different ailments[4] andwound healing[5].

Some of thetraditional claims have been investigated Scientifically using animal model and the efficacy has been proven[6,7]. Recent studiesshowed that *Carica papaya*leaf extract has been found to havepotential anti sickling (inhibition of sickle cell formation)[7]and has protective effect againstgastric ulcer in rats[6]. The flowers areknown to have antibacterial activities[8]. Oral administration of the seed extract could inducereversible male infertility and could be used forpharmaceutical development of a male contraceptive[9].

Literature on the effect of *Carica papaya* leaf extract on the kidney function and histology is scanty[10] and studies on the direct effect of aqueous extract of *Carica papaya* seedon the organis scarce.

Carbon tetrachloride(CCl_4) is a well known toxicant to both the liver and kidneys. It is said to induce an acute kidney damage by the formation of free radicals that causes oxidative stress.[11].

Therefore, the presentstudy is to investigate the effect of aqueous extract of *Carica papaya* seeds on the kidney function markers in CCl_4 induced renal toxicity inadult Wistar rats.

2. Materials and Methods

2.1. Plant Authentication and Extract Preparation

Carica papaya fruit was bought from a local market in Abraka, and was authenticated at the Botany Department, Delta State University, Abraka. The fruit was peeled and the seeds were collected, air dried and later grounded. Then

* Corresponding author:
drezekingx@yahoo.com (Eze Kingsley Nwangwa)
Published online at http://journal.sapub.org/als

they were weighed, 170 g of the grounded seed were soaked with 2000ml of distilled water for 72 hours and the residue was separated from the solvent. The solvent was concentrated to a paste like solid with a heating mantle yielding 36g. The extract was kept in a clean container and refrigerated until use.

2.2. Animal Handling

Thirty male Wistar albino rats (200 – 305g) obtained from the Animal house of the Faculty of Basic Medical Sciences, University of Benin, Benin City, were used for the study. They were kept in rat cages in a well-ventilated house, at the Animal House of the Faculty of Basic Medical Sciences, Delta State University. They were exposed to 12 hours light and 12 hours darkness and fed with clean tap water and rat chow once daily (8.00am - 9.00am). They were allowed to acclimatize for fourteen (14) days prior to the experiment.

2.3. Chemical and Reagent

Carbon tetrachloride, reagents and kits for analysis of kidney function markers were obtained from Sigma (USA) and they were of good analytical grade.

2.4. Extract Administration

The administration of the extract was done orally with the help of an orogastriccanulla once daily between the hours of 0900am and 1000am for a period of 28 days.

2.5. CCl_4 Induced Acute Kidney Damage

To induce renal toxicity CCl_4 was administered intra peritoneally (IP) at a dose of 0.8mg/kg as a 30% solution daily for 28 days..

2.6. Experimental Design

A total of thirty (30) Wistar albino rats were randomly divided into five groups of six rats each.

Group A:(Control) fed with rat chow and water ad libitum

Group B:fed with rat chow, water ad libitum and received 0.8mg/kg CCl_4

Group C:fed with rat chow, water daily, 0.8mg/kg $CCl_4$and then received dose of 100mg/kg of aqueous extract of C. *papaya* seeds.

Group D:fedwith rat chow, water daily, 0.8mg/kg $CCl_4$and then received dose of 200mg/kg of aqueous extract of C. *papaya* seeds.

Group E:fed with rat chow, water daily, 0.8mg/kg CCl_4 and then received a dose of 300mg/kg of aqueous extract of C. *papaya* seeds.

2.7. Collection of Samples

The rats were sacrificed by decapitation after an over-night fast. Blood samples were collected from the heart by cardiac puncture and put in a plane sample bottle and the serum was stored until used for analyses.

2.8. Serum Biochemical Assay

In the assessment of serum urea, creatinine, and electroly tes blood samples were obtained directly from theheart chamber of the ratsand were kept at the temperature of 4 °C for 2hours before they were centrifuged usingLaboratory Centrifuge (ModelSM 902B, Surgifriend Medicals, England,U.K.). The urea and creatinine levels in all the serum sample were estimated by modifiedmethods based on diacetyl monoximereaction[12] and Jaffe'sreaction[13],resp ectively, on standard diagnostic test kits (Randox Laboratories, Crumlin, U.K.)on Automated Clinical System (SychronClinical System®, model: CX5 PRO)(Beckman Coulter Inc., Galway, Ireland). The absorbance of samples was measured spectrophotometrically at 580nm against a reagent blank.

2.9. Ethical Considerations

Permission was granted by the Ethical Committee of the Delta State University, to carry out this study for the required period of time and the provisions of the declaration of Helsinki 1995 were complied with.

2.10. Statistical Analysis

Results were expressed as mean ± SD. The evaluation of data for statistical significance between control and experimental groups was done using one way ANOVA. The Turkey multiple comparison test was used to determine specific pairs of organs that were statistically different. Statistical software, SPSS 17, was used to analyze the data. A $P<0.05$ was accepted as statistically significant.

2. Results

Table 1. Effect of *Carica papaya*seed aqueous extract on the kidney function parameters and electrolytes of Wistar rats

Enzymes	Group A (Control)	Group B CCl4	Group C Cl4+ 100mg/kg	Group DCCl4 +200mg/kg	Group ECCl4+ 300mg/dl
Na+ (mg/dl)	140.00±8.08	208.20± 0.23*	133.00±12.7+	117.50±4.04*+	107.00±8.08+
K+(mg/dl)	5.35±0.06	3.25 ±0.02*	4.65±0.29	5.10±0.23+	5.15±0.06+
Cl- (mg/dl)	96.00±4.62	122.08± 072*	88.50±4.04+	80.20±4.04*+	72.50±4.04*+
Urea (mg/dl)	34.20±6.35	88.52± 0.15*	37.50±12.47+	45.45±1.21*+	47.55±5.25*+
Creatinine (mg/dl)	1.05±0.06	10.22± 0.45*	1.13±0.06+	1.15±0.06*+	1.25±0.06*+

In this study, changes in the levels of kidney function markers and electrolytes due to the effect of different doses of the *Carica papaya*seed aqueous extract on rats were compared to those of the control. The treated rats were administered with different doses of the extract after receiving CCl_4toxicant.

Values are presented as means ± SD; $P< 0.05$ compared with control group, $P< 0.05$ compared with group B (n=6)

The table above shows that administration of *Carica papaya*caused a dose-dependent and statistically significant decrease in the values of the kidney function markers and electrolytesinWistar rats,especially the dose of 200mg/kg and above. The aqueous extract of the plant seed caused a significant decrease ($P< 0.05$)in the Na^+,and Cl^- levels, and a non significant increase in K+ level, it also showed a significant reduction ($P< 0.05$) in the urea and creatinine compared with CCl_4 only treatment group (Group B)

3. Discussion

The use of CCl_4 to induce renal toxicity is well documen ted. CCl_4 has been shown to have hepatotoxic and nephroto xic potential[14].

Serum urea, creatinine and electrolytes are reliable and effective markers of renal function which could be indicative of the extent of the renal damage[15].

In this present study therefore, the use of the extract of *Carica papaya* seeds to modulate the effect of this nephroto xic substance is investigated. The findings confirmed the nephrotoxic potentials of CCl_4 as shown by the statistical significant ($P< 0.05$) increase in all the parameters of renal function markers (Group B) except for potassium which showed a significant decreased level compared with the control (Group A).

Furthermore, this study showed a dose-dependent statisti cally significant ($P< 0.05$) decrease in the renal function markers (urea, creatinine and electrolytes) in the groups administered with 100mg/kg, 200mg/kg and 300mg/kg of the extract of *Carica papaya* seeds compared with theCCl_4 only administered group (Group B) except for potassiun that showed a non-significant increase compared with the CCl_4only treated group.

Production of free Oxygen radical is one of the theories that explain the mechanism of cell injuries and damage and the presence of antioxidants have been found to be very useful in modulating the destruction. The phytochemical analysis of *Carica papaya* seeds extract is documented to contain alkaloids,saponin, vitamin B_{12}, vitamin C, antioxid ants, anthraquinonesetc[16].

Since CCl_4 produces its acute renal damage by causing oxidative stress through release of destructive free radicals, it is possible that the protective effect of *Caricapapaya*obse rved in this study may be a result of its antioxidant effect and/or free radicals scavenging effect which helps to detoxify the free radicals and reduce the lipid peroxidation arising from injury to cell membrane.

4. Conclusions

This study suggests that aqueous extract of *Carica papay a* seeds may have a nephroprotective effect on acute kidney damage especially if the mechanism of damage is by inducing oxidative stress. Therefore these findings need be further investigated for possible use in health care delivery.

ACKNOWLEDGEMENTS

The researcher wish to thank Augustine Godswill and EkhoyeEhitare for their contribution in this research work and the technical staff of the Department of Chemical Pathology, University of Benin Teaching Hospital, Benin Nigeria.

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