



ASN- PH-020919
ISSN: 2315-537X

International Journal of Herbs and Pharmacological Research

IJHPR, 2015, 4(4): 75 - 80

www.arpjournals.com; www.antrescentpub.com

E- ISSN: 2384-6836

RESEARCH PAPER

THE EFFECT OF CARICA PAPAYA SEED EXTRACTS ON UREA, CREATININE AND URIC ACID LEVELS IN WISTAR RATS.

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Received: 2nd July, 2015

Accepted: 25th September, 2015

Published: 31st October, 2015

ABSTRACT

This study investigated the effect of *Carica papaya* seeds on renal function parameters. Male Wistar rats aged 7± 1 weeks, and weighing 70.0-105.0g, were used for the study and the animals were divided into four groups -A, B, C and D. Group A served as control, while B, C and D, served as test groups. The test groups were further subdivided into three -B1 – B3, C1 – C3 and D1 – D3 (n=4 each) and they received a combination of both ripe and unripe *Carica papaya* seeds; ripe *Carica papaya* seeds only; and unripe *Carica papaya* seeds only, respectively. At the end of the experimental period of six (6) weeks, blood samples were obtained from the groups and analyzed for urea, creatinine and uric acid levels using standard methods. The statistical analysis of the data obtained was performed using the SPSS package (version 20) and results showed a dosage dependent and statistically significant increase in urea, creatinine and uric acid levels irrespective of the type; suggesting that *Carica papaya*'s has capacity to induce alterations in renal function. Thus, there is an urgent need to regulate the inclusion of *Carica papaya* seeds in herbal preparations; particularly in those used for the management of kidney diseases.

Key words: *Carica papaya*, Urea, Creatinine, Uric acid, Renal function

INTRODUCTION

A large and increasing number of populations use medicinal herbs or seek the advice of their physicians regarding the use of herbal products (O'Hara *et al.*, 1998). Available data indicate that more than half of the total population of the world use herbal drugs (Chang, 1987) and one such source of herbal preparations is *Carica papaya* (pawpaw) (Glombitza *et al.*, 1993). Studies have also shown that the fleshy part of the fruits of *Carica papaya* (mesocarp), has been identified to possess active ingredients with antioxidant, antimicrobial, anti-inflammatory, antiulcer, antidiabetic, antihypertensive and antihyperlipidemic potentials (Nor *et al.*, 2008). However, some other active substances in *Carica papaya*, like carpine and papain, have been found to be toxic (Eno *et al.*, 2000) and/or with anti-fertility properties (Lohiya *et al.*, 1999; Lohiya *et al.*, 1999; 2002; Pathak *et al.*, 2000); suggesting that the ingestion of *Carica papaya* seeds may adversely affect the fertility status of mammals.

Although there are lots of evidence confirming that the measurement of serum levels of the nitrogenous waste products like creatinine, urea and uric acid in blood, are useful in the diagnosis of renal failure (Deepak *et al.*, 2001; Allen, 2012), it is important to note however, that the administration of aqueous root extracts of *Carica papaya* to

adult male Sprague – Dawley rats, induced an increase in diuretic activities and urine output (Sripanidkulchai *et al.*, 2001).

Regrettably, the effects of *Carica papaya* seeds on renal parameters are yet to be fully understood (Olagunjua *et al.*, 2009) and there exists an information deficit on the dimensions of its effects in ripe and unripe states, or both in combination. This study therefore, was designed to determine the effects of *Carica papaya* seeds in various states - ripe and unripe, or in combination, on urea, creatinine and uric acid levels in Wistar rats.

MATERIALS AND METHODS

Experimental Animals: Forty (40) male Wistar rats (7±1 week old) of comparable sizes and weights ranging from 70.0g to 105.0g, were procured from the animal house of the College of Medicine, Ambrose Alli University, Ekpoma, Nigeria, and moved to the site of the experiment at Saint Mary's Road, Ekpoma, Edo State, Nigeria, where they were acclimatized for 2 weeks. During the period of acclimatization, the mean average feed per day was observed to be 61g.

Animals Grouping: The experimental animals were divided into four major groups -A, B, C and D. Group A served as control, while groups B, C and D, served as test groups. The test groups were further subdivided into three subgroups as follows:

1. Groups B1, B2 and B3
2. Groups C1, C2, and C3
3. Groups D1, D2 and D3

Sub groups B1, C1 and D1 served as the main test groups while Sub B2, B3, C2, C3, D2 and D3 served as the test control groups.

The animals were housed in well ventilated wooden wire mesh cages designed to secure the animals properly, especially from wild animals and insects. They were fed with 61g of feed and water was given *ad libitum*. As described by Bolu *et al.* (2009), the weight of the animals were determined on the first day of acclimatization and then weekly, throughout the period of study.

Substance of Study: Ripe and unripe *Carica papaya* fruits were purchased from Ekpoma main market, and authenticated by a botanist in the Department of Botany, Faculty of Natural Science, Ambrose Alli University, Ekpoma, Edo State, Nigeria.

Substance Preparation: The ripe and unripe *Carica papaya* (CP) fruits were cut open to harvest the seeds which were subsequently sun-dried separately. The dried seeds were then crushed into fine powder using an electric blender. The fine powder was measured using an Electric Balance (Denver Company, USA, 200398. IREV.CXP-3000) and packaged in small plastic envelopes and then stored pending usage. The feeds (grower mash) produced by Grand Cereals Ltd -a subsidiary of UAC of Nigeria Plc, Jos, Plateau State, were weighed using a goat scale weighing balance (China). For the purpose of this study, pellets were prepared by adding measured quantities of *Carica papaya* to the feed (grower's mash) as described by Nwaopara *et al.* (2011).

Substance Administration: Group A (control) received 61g of feed and distilled water only, while the test and test control groups received graded doses of *Carica papaya* (CP) seed powder as described below:

Group B1 (test group) received a combination of 2g of ripe and unripe CP, while groups B2 and B3 (test controls) received 2g of ripe and 2g of unripe CP plus 59g of feed and distilled water respectively.

Group C1(test group) received a combination of 4g of ripe and unripe CP, while groups C2 and C3 (test controls) received 4g of ripe and 4g of unripe CP plus 57g of feed and distilled water respectively.

Group D1 (test group) received a combination of 6g of ripe and unripe CP, while groups D2 and D3 (test controls) received 6g of ripe and 6g of unripe CP plus 55g of feed and distilled water respectively.

Sample Collection: Blood samples were obtained upon dissection, from the femoral vein of each of the animals in the groups into a well labeled lithium heparin bottles. The blood samples were then transported to the chemical pathology Departments of Irrua Specialist Teaching Hospital, Irrua, Edo State, Nigeria, for the determination of

serum creatinine, urea and uric acid levels, using methods described by Fabiny and Ertingshausen, (1971) and Cheesbrough (2005).

Statistical Analysis: Data were analyzed using the Scientific Package of Social Sciences (SPSS; version 20) and values were expressed as mean \pm standard deviation. Specifically, the student paired sample t-test was used for comparative statistics and the observed differences were considered significant at $p < 0.05$.

Study Duration: The preliminary studies, animal acclimatization, substance procurement (*Carica papaya* procurement and preparation, actual animal experiment and evaluation of results, lasted from June 2015 to November, 2015. However, the actual administration of the prepared *Carica Papaya* seed powder to the test animals lasted for 6 weeks.

RESULTS

Results of the paired sample analysis t-test and correlation showed that the mean creatinine level for the control group was 1.25mg/dl. Comparatively, there were decreased levels of creatinine in the test groups especially in group D1 (1.08 mg/dl), followed by B1 (1.13mg/dl) and then C1 (1.20mg/dl) (see table 1). Similar decreased levels of creatinine was observed in groups B2, C2 and D2 (1.0250mg/dl; 1.13mg/dl; and 1.08mg/dl respectively) (see table 2) as well as in groups B3 and D3 (1.15mg/dl apiece). Only group C3 posted an increase in creatinine levels (1.48 mg/dl). The observed differences were statistically significant in groups B1, B3 and C3 (see table 1 and 3).

Table 1: Mean Creatinine, Urea and Uric Acid Levels in Control and Test groups B1, C1 and D1

Group	Creatinine mg/dl)	Urea(mg/dl)	Uric Acid(mg/dl)
A	1.25 \pm 0.13	36.25 \pm 11.35	2.15 \pm 0.37
B1	1.16 \pm 0.10 ^a	32.25 \pm 6.13*	2.25 \pm 0.33
C1	1.20 \pm 0.08	31.75 \pm 2.22*	1.67 \pm 0.47
D1	1.08 \pm 0.10	41.25 \pm 2.99*	1.78 \pm 0.49

Values are expressed as Mean \pm Standard deviation; (*) significantly different in the paired sample test; (^a) significantly different in the paired sample correlation statistics

Also, decreased levels of urea were observed in groups B1 and C1 (32.25mg/dl and 31.75 mg/dl respectively) but an increase in group D1 (41.25 mg/dl). Similarly, decreased levels of urea were observed in group B2 (32.75 mg/dl), while C2 and D2 posted a drastic increase in the levels of urea (39.00mg/dl and 40.50 mg/dl) respectively, compared to the control group value of 36.25 mg/dl. The results from group B3 also showed decreased levels of urea (32.50 mg/dl), but groups C3 and D3 posted increased levels of urea (39.25mg/dl and 42.75mg/dl respectively) as compared to the control group value of 36.25 mg/dl. The observed differences in the levels of urea were statistically significant for both the paired sample t-test (B1, C1 and D1) and paired sample correlation statistics (D3) (see table 1 and 3).

Finally, the results on uric acid levels in groups B1, C1 and D1 indicated that uric acid levels increased in B1 (2.25 mg/dl) but decreased in C1 (1.67mg/dl) and D1 (1.78mg/dl). Similarly, there was an increase in the uric acid levels in group B2 (2.23mg/dl), but a decrease in C2 and D2 (1.68mg/dl and 1.78 mg/dl respectively) as compared to the control group value of 2.15mg/dl. However, only a slight increase in the uric acid levels in group B3 was observed (2.18 mg/dl), but C3 and D3 clearly posted decreases in uric acid levels (1.73mg/dl and 1.95 mg/dl respectively) as compared to the control value of 2.15 mg/dl, and the differences observed were statistically significant in group B2 (see table 3).

Table 2: Mean Creatinine, Urea and Uric Acid Levels in Control and Test groups B2, C2 and D2

Group	Creatinine(mg/dl)	Urea(mg/dl)	Uric Acid(mg/dl)
A	1.25±0.13	36.25±11.35	2.15±0.37
B2	1.03±0.15	32.75±5.32	2.23±0.86 ^a
C2	1.13±0.21	39.00±2.31	1.68±0.15
D2	1.08±0.10	40.50±7.94	1.78±0.52

Values are expressed as Mean ±Standard deviation; (^a) significantly different in the paired sample correlation statistics

Table 3: Mean Creatinine, Urea and Uric Acid Levels in Control and Test groups B3, C3 and D3

Group	Creatinine (mg/dl)	Urea(mg/dl)	Uric Acid(mg/dl)
A	1.25±0.13	36.25±11.35	2.15±0.37
B3	1.15±0.24 ^a	32.50±4.51	2.18±0.42
C3	1.48±0.43 ^a	39.25±5.74	1.73±0.22
D3	1.15±0.05	42.75±2.06 [*]	1.95±0.47

Values are expressed as Mean ±Standard deviation; (^a) significantly different in the paired sample correlation statistics

DISCUSSION:

The outcome of this study significantly highlighted a trend that higher doses of unripe *Carica papaya* seeds –as exhibited in group C3, unlike the other test groups, can induce an elevation of creatinine levels, which by implication, suggests that unripe *Carica papaya* has a higher propensity to induce renal failure. Similarly, the observed increase in the creatinine levels of group D1, compared to the decrease in B1 and C1, indicate that at a higher dose, the combination of ripe and unripe *Carica papaya* seeds may trigger an elevation in the levels of urea compared to the observations in B1 and C1. In addition, the observed increase in the values of urea in groups C2, D2, C3 and D3, compared to the observed decrease in groups B2 and B3, suggests that at higher doses, *Carica papaya* has capacity to induce the reduction of urea irrespective of its state –ripe or unripe. Most importantly, the observed increase in the values of urea in group D1 signifies that the inclusion of the ripe seeds in B1 and C1 may account for the moderations in the levels of urea. Also, the observations that uric acid levels decreased in C1, D1, C2, D2, C3, D3 as against the increase observed in groups B1, B2 and B3, implied that *Carica papaya* at higher doses, irrespective of its state –ripe or unripe, or in combination, can induce the reduction of uric acid levels.

Being conscious of the fact that serum urea, creatinine and uric acid levels are indicative of the extent of renal damage (Glombitza *et al.*, 1993; Feig, 2009; Mazzali *et al.*, 2002), our results surely indicated that *Carica papaya* had influence on the serum levels of the renal biomarkers and by extension, the functional performance of the kidney. In specific terms, the observed significant increase ($p < 0.05$) in the levels of urea, creatinine, and uric acid levels across the groups is consistent with earlier findings reported by Glombitza *et al.* (1993) that rats treated with *Carica papaya* seed extract, showed increased serum levels of urea, creatinine and uric acid, but contradicts the report by Indran *et al.* (2008) that renal biomarkers were not significantly affected following an exposure to aqueous *Carica papaya* seed extract for 2 weeks. The contradiction with the later report however, might be due to differences in the mode administration, nature of the substance in question, and the duration of study which in this case, was 6 weeks.

Furthermore, the observed dosage-dependent decrease in renal biomarkers and the comparative differences in the levels of urea and uric acid, particularly in group D1 (1.08mg/dl and 1.78mg/dl respectively), is consistent with the observations made by Eze (2012) that there is a dose dependent and statistically significant decrease in renal biomarkers in subjects treated with higher doses of *Carica papaya* seeds extract, compared to the lower dose groups.

From the foregoing therefore, it is quite obvious that the dosage dependent and statistically significant increases in urea, creatinine and uric acid levels, irrespective of the type, indicates that *Carica papaya*'s has capacity to induce alterations in renal function. Thus, there is an urgent need to regulate the inclusion of *Carica papaya* seeds in herbal preparations, particularly in those used for the management of kidney diseases.

ACKNOWLEDGEMENT

The authors are sincerely grateful to individuals and organizations that made this study possible.

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AUTHOR'S CONTRIBUTIONS

The work was designed and supervised by Igbinovia, E.N.S. Isah, M played significant roles in data collection, tissue processing, data analysis and the drafting of the manuscript. All the authors participated in the editing and review of draft-manuscript.