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REVIEW PAPER

THE EFFECT OF *CARICA PAPAYA* SEED EXTRACT ON THE HISTOLOGY OF THE KIDNEY IN WISTER RATS

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ABSTRACT

This study was carried out to investigate the effect of ripe and unripe carica papaya seeds on the histology of the kidney in male Wister rats. The animals were divided into four groups -A, B, C and D, with group A serving as control, while groups 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 respectively) and the subgroups received a combination of 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, the animals were sacrificed to harvest the kidneys for histological studies. Microscopic examinations of the respective kidney tissue sections revealed dosage dependent cytoarchitectural distortions across the groups especially in group D, where severe hemorrhagic signs, glomerular shrinkage, inflammatory cell infiltration, tubular wall disruption, and glomerular degenerations were observed. The results suggests that *Carica papaya* seed can best be classified as a dosage-dependent nephrotoxic or non-nephrotoxic agent and its cautious inclusion in herbal drug therapy is unequivocally recommended.

Key-words: *Carica papaya*, chymopopain, kidneys, nephrotoxic, papain

INTRODUCTION

Carica papaya (CP) is a member of the plant family known as *Caricaceae* and commonly grown in the West Indies, Philippines, Sri Lanka, India, Bangladesh, Malaysia and other countries in Africa. When ripened, the fruit becomes light or deep yellow; with a thick succulent, fleshy and aromatic wall; to which numerous small, black, ovoid, corrugated, peppery seeds are attached lightly by soft white fibrous tissues (Maton *et al*., 1993). Of greater interest, are its biologically active compounds especially papain and chymopopain (Brocklehurt and Salih, 1985).

On the other hand, the kidneys are important pair of homeostatic organs involved in the removal of waste products of metabolism, as well as the regulation of electrolytes, maintenance of acid-base balance, and regulation of blood pressure via the regulation of salt and water balance (Salem and Eknoya, 1999). The Kidneys are also been known to produce hormones like calcitriol and erythropoietin, and an important enzyme called rennin (Sembulingam and Sembulingam, 2010).

Taking into consideration the role of the kidneys and its vulnerability to toxic insults on one hand, and the growing consumption of herbal preparations containing extracts of *CP* seeds on the other, this study therefore, investigates the comparative effects of ripe and unripe *Carica papaya* seed consumption on the histology of the kidney in male Wister 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 experimental 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 that the animals were able to consume was determined to be 61g.

Substance of Study: Both ripe and unripe *Carica papaya* fruits were purchased from Ekpoma main market, Edo State, Nigeria, 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).

Animals Grouping: The experimental animals were divided into four major groups (group A –Control; and B, C, and D –test groups). Each of the test groups were further subdivided three sub groups 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

Experimental design: The animals which were fed 61g of feed with water given *ad libitum*, were weighed on the first day of acclimatization and then weekly thereafter, throughout the period of experiment as described by Bolu *et al*. (2009). They were housed in well ventilated labeled wooden wire mesh cages at the site of the experiment. The cages were designed to secure the animals properly especially from wild animals/insects and cleaned on a daily basis.

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

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 and Analysis: Kidney tissue samples were obtained upon dissection from each of the animals in the groups and fixed in sterile universal bottles containing 10% formol saline solution. They were then transported to the Histopathology Laboratory at Irrua Specialist Teaching Hospital, Irrua, Edo State, Nigeria, for routine tissue processing and staining with Heamatoxylin and Eosin. The histological examination (with micrography) of the prepared slide was read under a binocular microscope in the Department of Anatomy, Faculty of Basic Medical Sciences, College of Medical Sciences, Ambrose Alli University, Ekpoma.

RESULTS:

The histological finding revealed normal cytoarchitectural features of the kidney with intact parenchyma and distinct Bowman's capsule around the visible glomeruli in the control tissue sections (*see* plate 1). However, cytoarchitectural alterations were observed in the kidney sections of the test groups and the alterations were consistent irrespective of the seed type, but the changes were more pronounced in groups D1 indicating a dosage dependent phenomenon. The observations include:

1. Distortions in the tubular epithelial wall of test group B1 Kidney sections (*see* plate 2)
2. Hemorrhagic signs with glomerular shrinkage and vacuolations in test group B2 Kidney sections (*see* plate 3).
3. Glomerular shrinkage and vacuolations in test group B3, C1, C2 and C3, Kidney sections respectively (*see* plates 4, 5, 6, 7, 8 and 9).
4. Severe hemorrhagic signs with severe inflammatory cell infiltration and glomerular shrinkage and vacuolations in test group D1 Kidney sections (*see* plates 10, 11 and 12).
5. Tubular wall disruption with glomerular shrinkage in test group D2 Kidney sections (*see* plate 13).
6. Glomerular shrinkage and vacuolations in test group D3 Kidney sections (*see* plate 14, 15 and 16).

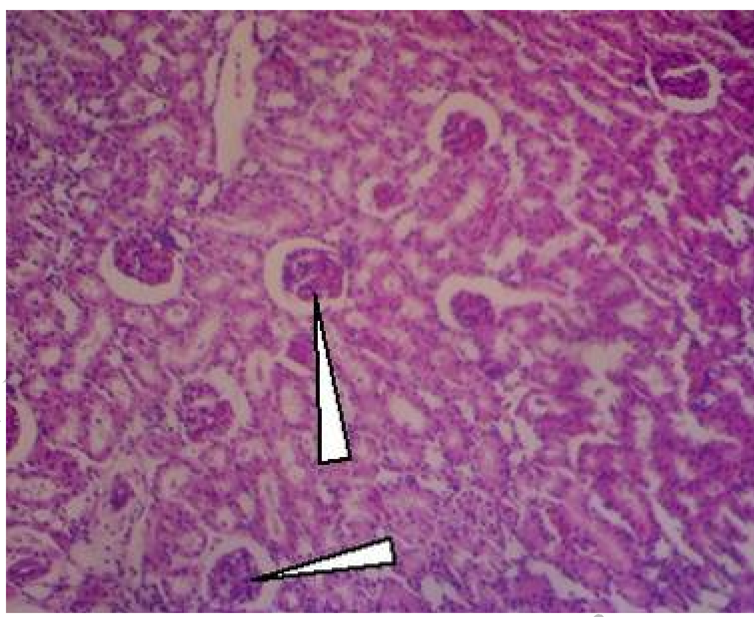

Plate 1: Photomicrograph of Control Kidney section (H&E x100) showing normal cytoarchitectural features of the Kidney with intact parenchyma and distinct Bowman's capsule around the visible glomeruli (white arrows)

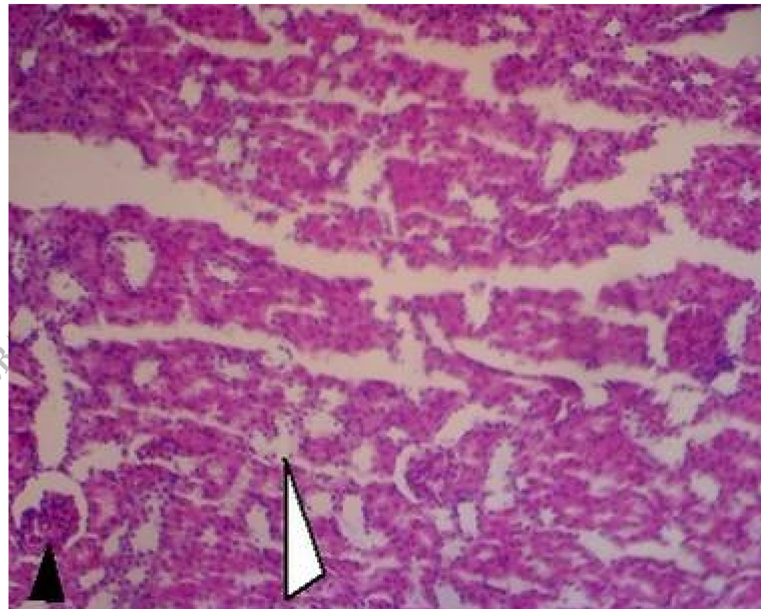

Plate 2: Photomicrograph of test group B1 Kidney section (H&E x100) showing distortions in the tubular epithelial wall (white arrow) with signs of glomerular shrinkage (black arrow)

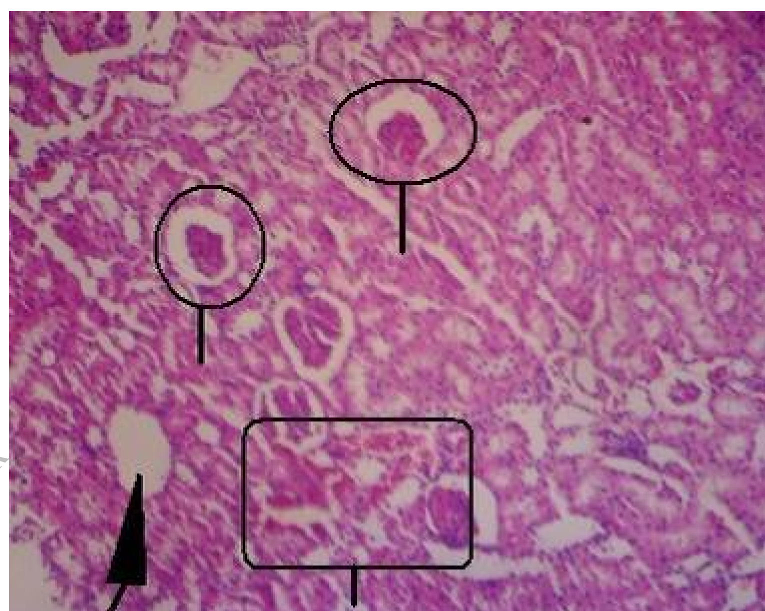

Plate 3: Photomicrograph of test group B2 Kidney section (H&E x100) showing hemorrhagic signs (in square shaped 'lens'), glomerular shrinkage (see round 'lenses') and vacuolations (see black arrow).

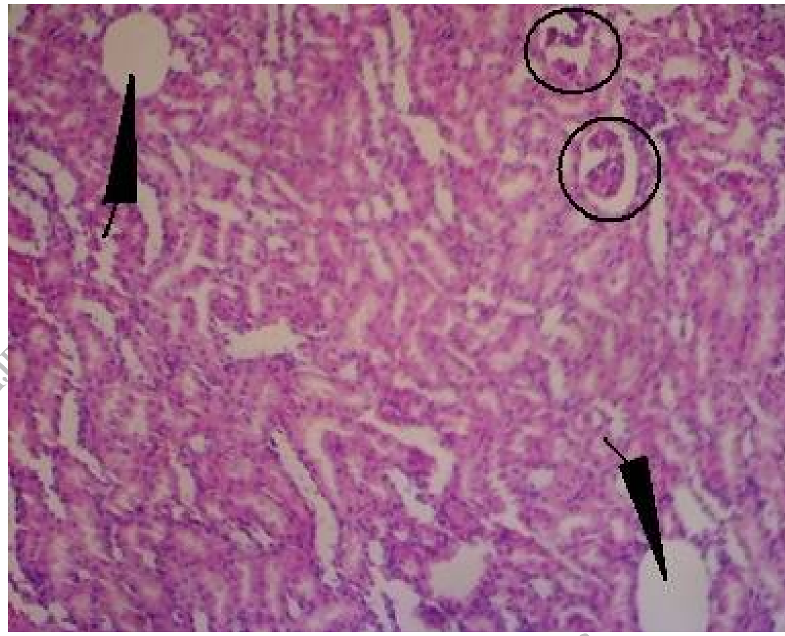

Plate 4: Photomicrograph of test group B3 Kidney section (H&E x100) showing glomerular shrinkage (encircled) and vacuolations (see black arrows).

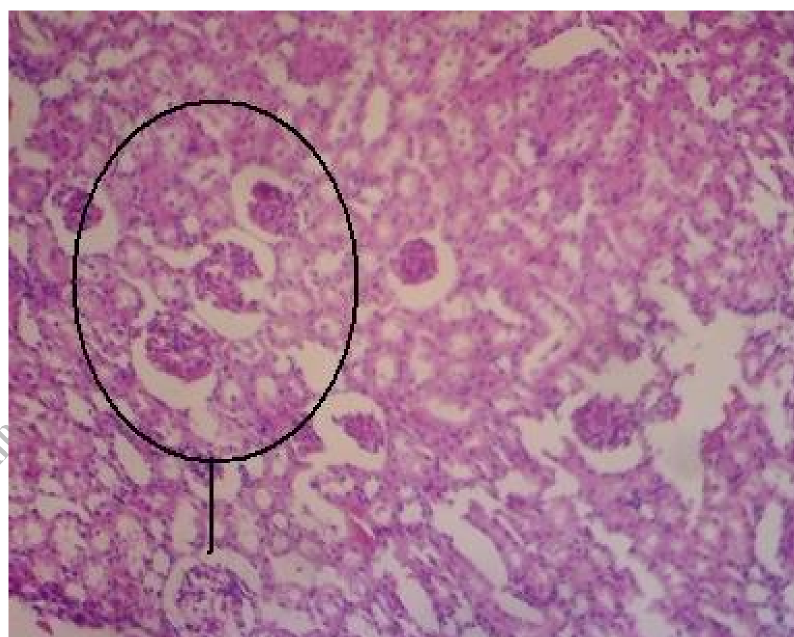

Plate 5: Photomicrograph of test group C1 Kidney section (H&E x100) showing signs of glomerular shrinkage (see round 'lens')

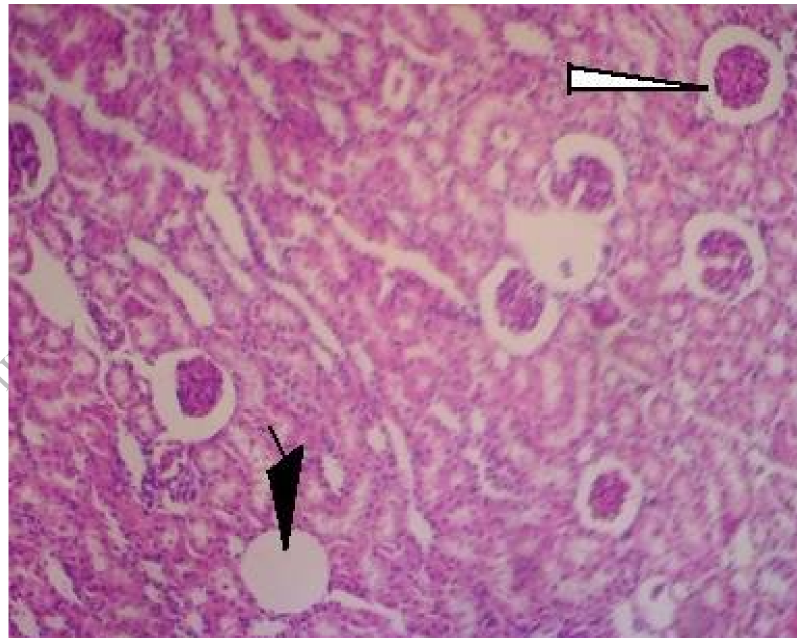

Plate 6: Photomicrograph of test group C2 Kidney section (H&E x100) showing glomerulus (white arrow) and vacuolations (see black arrow).

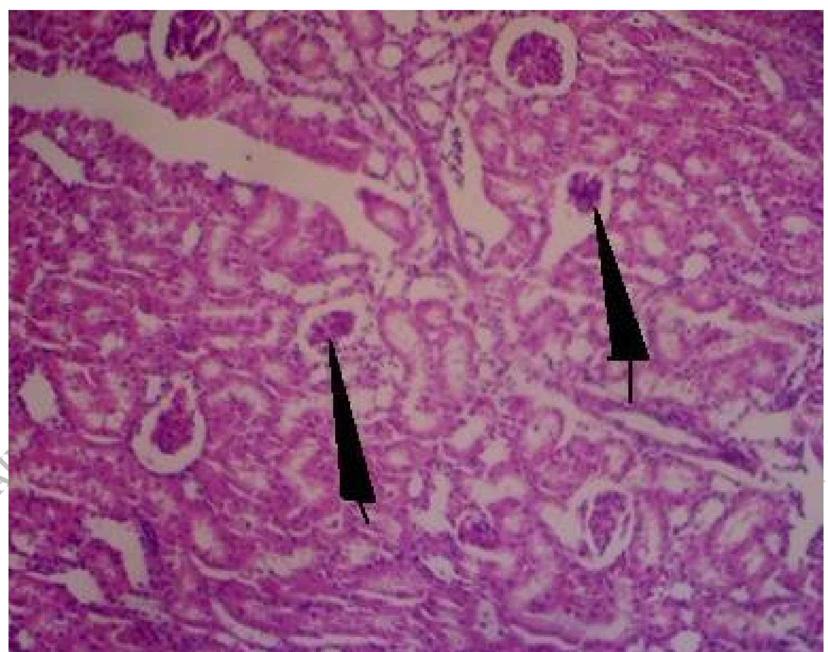

Plate 7: Photomicrograph of test group C2 Kidney section (H&E x100) showing degenerative glomerular shrinkage (see black arrows).

Plate 8: Photomicrograph of test group C3 Kidney section (H&E x100) showing degenerative glomerular shrinkage (see round 'lens').

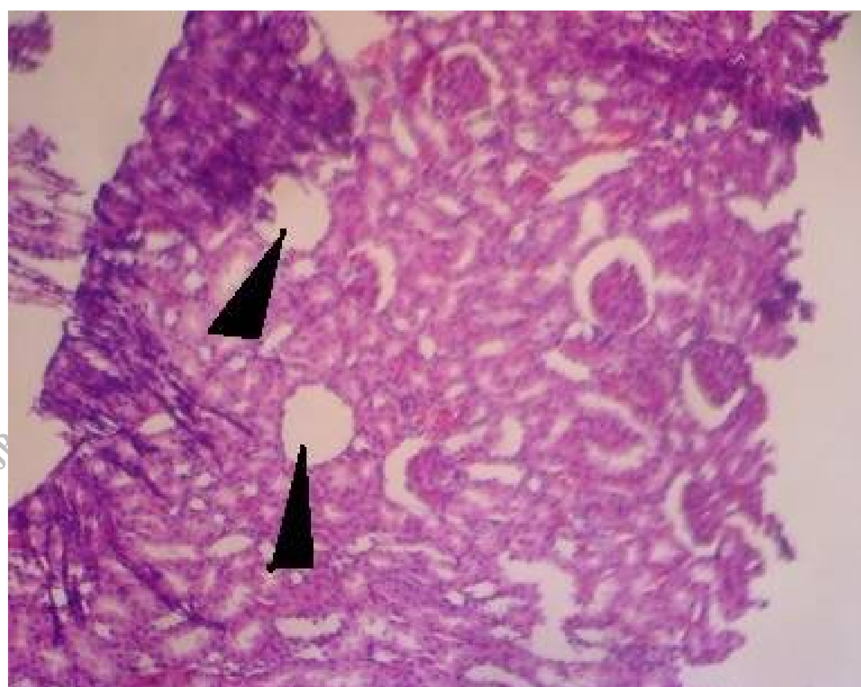

Plate 9: Photomicrograph of test group C3 Kidney section (H&E x100) showing vacuolations (see black arrows).

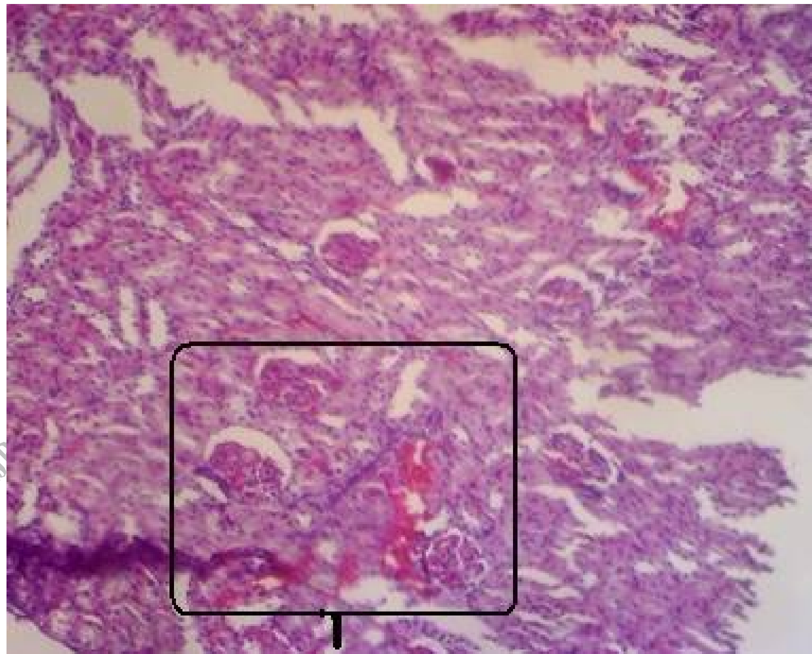

Plate 10: Photomicrograph of test group D1 Kidney section (H&E x100) showing severe heamorragic congestions (see square 'lens').

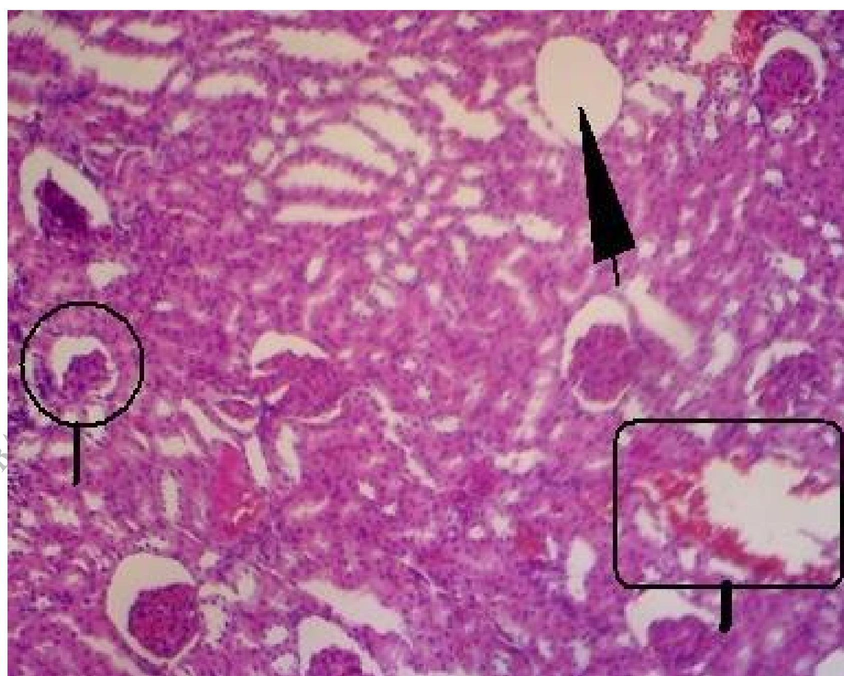

Plate 11: Photomicrograph of test group D1 Kidney section (H&E x100) showing severe hemorrhagic congestions (see square 'lens'), glomerular shrinkage (see round 'lens') and degenerative vacuoles (see black arrow).

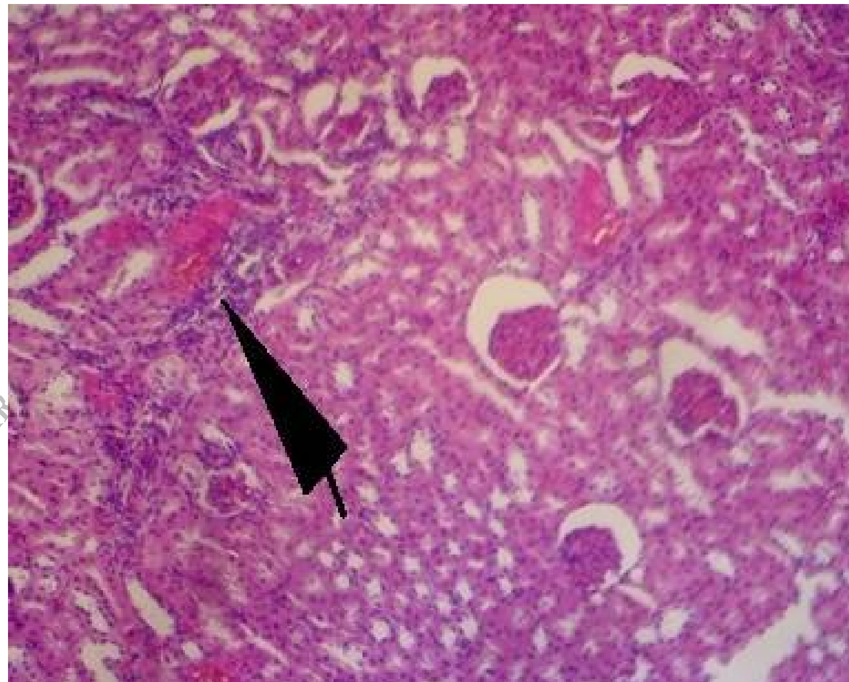

Plate 12: Photomicrograph of test group D1 Kidney section (H&E x100) showing severe inflammatory cell infiltration (see black arrows)

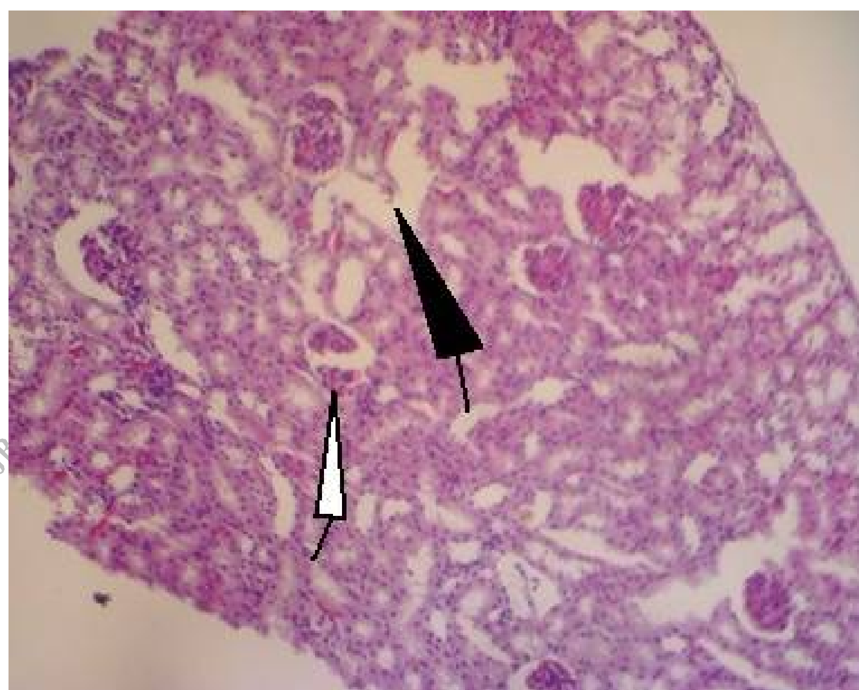

Plate 13: Photomicrograph of test group D2 Kidney section (H&E x100) showing tubular wall disruption (see black arrows) and glomerular shrinkage (white arrow)

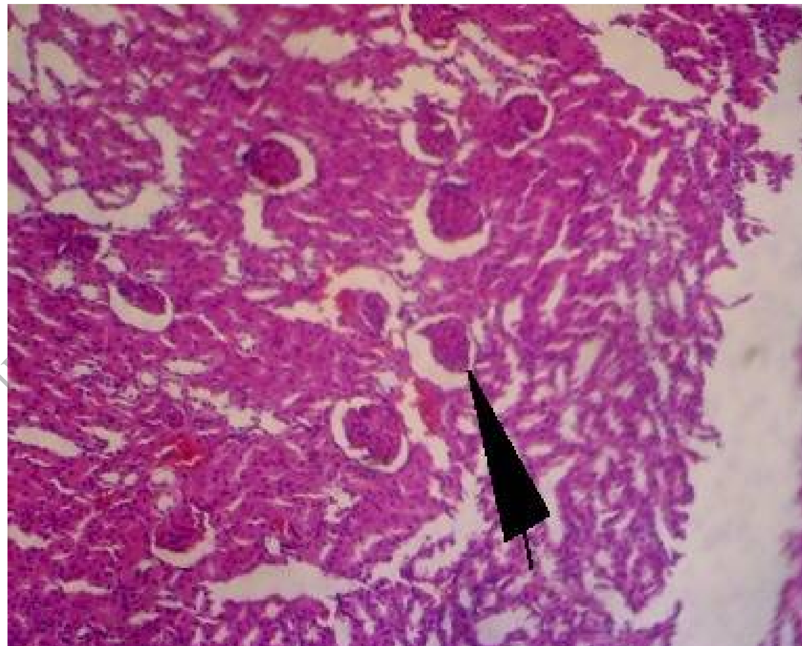

Plate 14: Photomicrograph of test group D3 Kidney section (H&E x100) showing glomerular shrinkage (see black arrow)

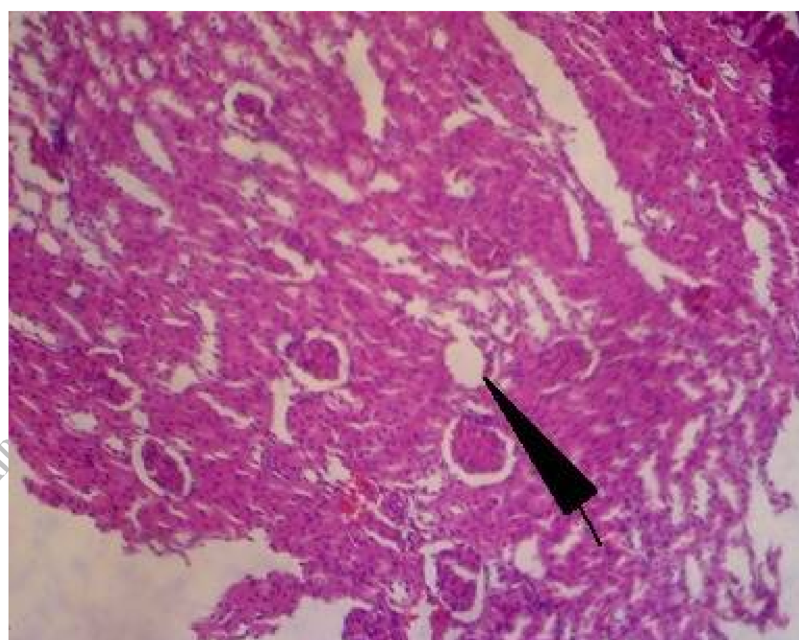

Plate 15: Photomicrograph of test group D3 (B) Kidney section (H&E x100) showing degenerative vacuoles (see black arrow).

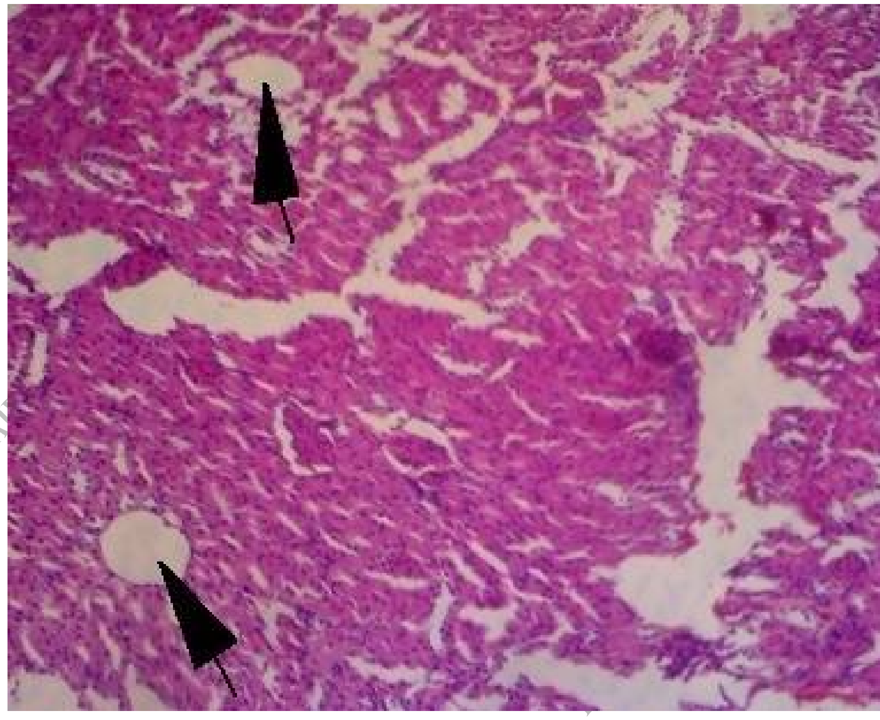

Plate 16: Photomicrograph of test group D3 Kidney section (H&E x100) showing degenerative vacuoles (see black arrows).

DISCUSSION:

The histological findings of this study apparently contradict the widely reported nephroprotective potentials of Carica papaya (Umana *et al*., 2013; Nale *et al*., 2012; Olagunju *et al*., 2009). This contradiction can be justified by the differences in the mode of administration and probably and the dosage of *Carica papaya* administered. While this study adopted oral administration of the *Carica papaya* seeds, these cited studies opted for the extracts. On the other hand the quantities of carica papaya seeds administered in grams, outweighs the quantities administered in the cited studies (in milligrams). These comparative differences in methodology may therefore, account for the observed contradictions in the nephroprotective potentials of *Carica papaya*, since dosage has been identified as a significant factor in conferring either "poisonous" or "non-poisonous" status on any given substance. In fact, Udoh *et al*. (2005) had asserted earlier that hydro-methanolic seed extract of *Carica papaya*, may not cause significant histological alterations when administered in low doses.

Other studies however, have reported the nephrotoxic activities of some active ingredients of *Carica papaya*. Such is the report by Mojica-Henshaw (2003) that *Papain*, an active ingredient of *Carica papaya,* has nephrotoxic activities and the phenomenon may explain the findings of this study. In fact, Yao *et al*. (2007), had argued that the observed glomerular damage may have resulted from sodium, potassium and magnesium loss, while the observed heamorrhagic changes and inflammatory cell's infiltration may probably be due to the concomitant influence of *Carica papaya* on the liver considering its hepatotoxic potentials (Liebert *et al*., 2005); though Schmidt *et al.* (2007) and Oduola (2007) had stated that *Carica papaya* seed extract consumption did not induce hemorrhagic effects on the kidneys in Wistar rats.

On the whole, the findings of this study does indicate that the observed alterations in the cytoarchitecture of the kidney, were independent on the state of the seeds (ripe or unripe); thereby supporting the assertion by Olagunju *et al*. (2009) that unregulated inclusion of *Carica papaya* may not be suitable in herbal preparations. It is also obvious that *Carica papaya* seed can best be regarded as a dosage-dependent nephrotoxic agent; the need for caution in the inclusion in herbal drug therapy is unequivocally recommended.

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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.