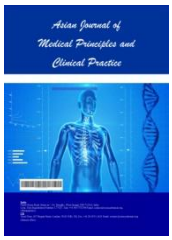

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Effect of *Morinda Lucida* Leaf Extract on Ibuprofen Induced Nephrotoxicity Albino Rats

Nkiruka Millicent Amadi[1], Peter Uwadiegwu Achukwu[2], Emmanuel Ifeanyi Obeagu[3*] and Nonyelum V. Anoh[1]

[1]Department of Medical Laboratory Science, Enugu State University of Science and Technology, Enugu State, Nigeria.
[2]Department of Medical Laboratory Science, University of Nigeria, Enugu Campus, Enugu State, Nigeria.
[3]Department of Medical Laboratory Science, Imo State University, Owerri, Imo State, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Morinda lucida ethanol stem bark extract dilution of ((500, 1000, 1500) mg /kg) body weight were administered to B_1, B_2, B_3 groups subjected to ibuprofen induced nephrotoxicity. Histomorphological studies on target organ; kidney were harvested, weighed and processed. Ibuprofen toxic activities of the extracts treated groups (serum biochemical markers) and the relative organ index ($\rho<0.05$) in treated groups respectively produce significant changes. Target organ extract examinations offered some protection on glomerular and tubular degenerative changes while there are deterioration changes in B groups.

Keywords: Toxicity; Ibuprofen; Kidney; nephrotoxicity; albino rats.

**Corresponding author: E-mail: emmanuelobeagu@yahoo.com;*

1. INTRODUCTION

Morinda lucida is a medicinal plant of West African rainforest belong to species in the Genus of Morinda of the pyroidea family from Rubiaceae with these common names in Nigeria Nfia or ogere in Igbo, Oruwo or Ruwo in Yoruba and Idonzakara in Hausa. It is a multipurpose active component of medicinal plant used in Nigeria to reduce health challenges like hypoglycermia, hypertension, malaria, infections analgesic [1-3]. It was also reported that *Morinda lucida* stem bark extract indicated significant of some pharmacological components, alkaloid, tannins, flavonoid, saponins, phenol, triterpenoid, phlobatannins; while cardiac glycosides, steroid glycosides anthraquinones and garlic tannins where insignificant [4].

Kidney consists of a functional unit with numerous nephrons that is composed of renal corpuscle and tubules; the capsule is made up of dense connective tissue covering the kidney; renal pelvis contain hilum which is composed of entrance and exit structures for supply and removal of substances from the kidney such as, blood vessels, ureters, nerves and lymphatic [5-6]. Renal toxicity implies drug or chemically derived damage caused by toxin or drug ingestion leading to abnormality in the kidney, thus hindering its ability to function [7]. This may result in renal dysfunction such as acute or chronic interstitial nephritis, glomerulonephritis, acute tubular necrosis, acute kidney injury (AKI) [8].

2. MATERIALS AND METHODS

2.1 Plant Sample Collection and Identification

Morinda lucida stem barks were collected from farmland in Enugu east metropolis of Enugu state, Nigeria between the month of March and April 2020. The plant part samples were taken to the herbarium for authentic identification and characterization at Plant Science and Biotechnology Department of University of Nigeria Nsukka with a voucher specimen number (UNH No. 299).

2.2 Animal Husbandry

Albino rats were collected from the animal house Enugu State College of Medicine, Parklane. The animals were housed in a clean gauzed cage, fed on pellet feed, clean tap water and kept under standard condition. The experiments were conducted with due care and diligence according to the institutional regulation guidelines of the use of animals.

2.3 Crude Extract Preparation Procedures

The stem bark of the plant cleaned, air dried, finely grounded into powder using a grinder and put in an airtight to avoid contamination.

Ethanol Extractions (E): Various *Morinda lucida* parts extracts were prepared by immersing 250 g of respective parts powder into to 1000 ml of 80% ethanol respectively before subjection to the following model:

1. The ethanol extractions were left for 72 hrs at room temperature.
2. Resultant crude extractions were obtained by first filtration through the muslin cloth; then further filtrations through Whatman No. 1 filter paper.
3. The filtrates were concentrated using an evaporator set at 40^0 C.
4. Each jelly concentrate obtained was placed in a well labeled plastic container and stored in a refrigerator at 4^0 C until required.

Studies on *Morinda lucida* ethanol stem bark extract on Ibuprofen induced kidney damage albino rats were conducted using protective experimental design as shown below.

Animals: Mature adult rats of mixed sexes with body weight 150-200g were used in conducting the study.

Drugs and chemicals: Valfen (Ibuprofen) tablets 400mg manufactured by Mancare Pharmaceutical PVT LTD Maharashtra, India was purchased from Arluc pharmaceutical shops Trans- Ekulu, Enugu State, Nigeria. The drug tablets were crushed into fine powder to gavage 50 mg/kg body weight.

Ethanol Stem Bark Extracts Preparation: *Morinda lucida* ethanol stem bark extractions were obtained as stated above.

2.4 Experimental Treatment Design

Oral daily administration of 50mg/kg body weight of Ibuprofen for 42 days were introduced to

induce a significant renal tissue injury and kidney dysfunction to group B, B_1, B_2, and B_3 [9].

1. Group B_1, B_2, B_3 received concentrations of the ethanol stem bark extract of ((500, 1000 and 1500) mg/kg) body weight respectively with Ibuprofen for 42days.
2. Group B (25 rats) received only Ibuprofen for 42days (positive control)
3. Group B_0 (5rats) received only water for 42days.
4. Group B_X and B_S(5rats each) received concentrations of the ethanol stem bark extract of ((1000 and 1500) mg/kg) body weight respectively

On Day 43, five (5) rats in each Group were sacrificed

2.5 Curative Stage

I. On Day 43, Group Bwere sub divided into BA_1, BA_2, BA_3 (5rats each).
II. BA_1, BA_2, BA_3 (treatment groups) received different extract concentrations of ((500, 1000 and 1500) mg/kg) b. wt respectively for14days [10].

2.6 Body Weight Measurement

Body weight (grams) of each rat was recorded on Day 0 of the course of the study. The average body weight for each group was calculated and recorded.

2.7 Biochemical Analysis

At the end of the study (Day 43), blood samples were collected and serum obtained for biochemical parameters (kidney marker) analysis. Albumin, Urea and Creatinine were analyzed using automation methods.

2.8 Histopathological Studies

The rats were anaesthetized and sacrificed; harvested kidney were visually inspected for macroscopically changes; processed according to histological techniques for histomorphological studies using Haematoxylin and Eosin methods.

2.9 Statistical Analysis

Data were statistically analyzed to determine effects of the drug on treated groups and student's t-test were used for comparisons. $P<0.05$ was considered statistically significant.

3. RESULTS

3.1 Histomorphological Findings

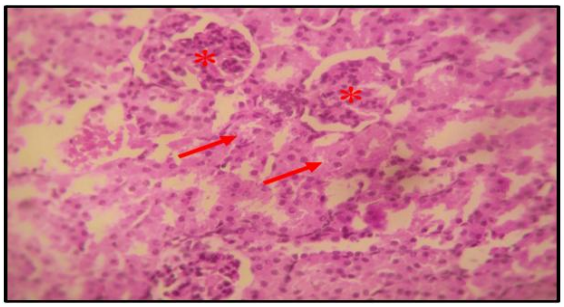

Fig. 1. Kidney section from group B_X. The glomeruli (*) and tubules (arrow) are normal. Stain: Haematoxylin and Eosin. Magnification: X100

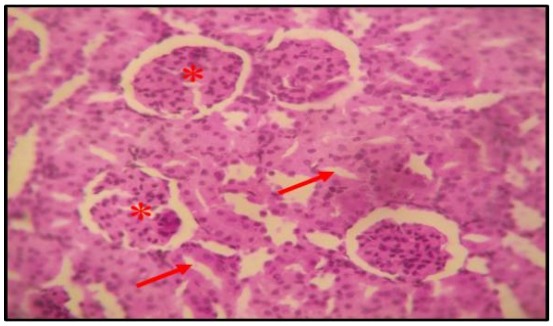

Fig. 2. Kidney section from group B_S. The glomeruli (*) and tubules (arrow) are normal. Stain: Haematoxylin and Eosin. Magnification: X100

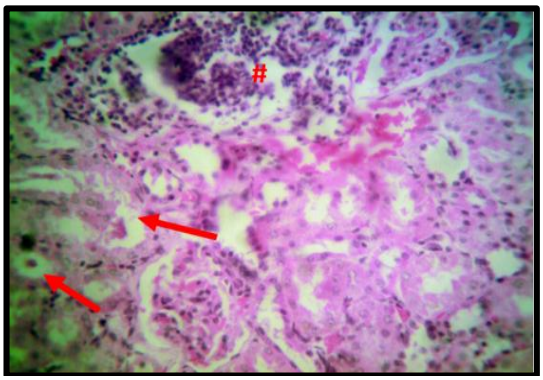

Fig. 3. Kidney section from group B showing a constricted glomerulus (#) and some renal tubules contain an eosinophilic cast (arrow). Stain: H&E. Magnification: X100

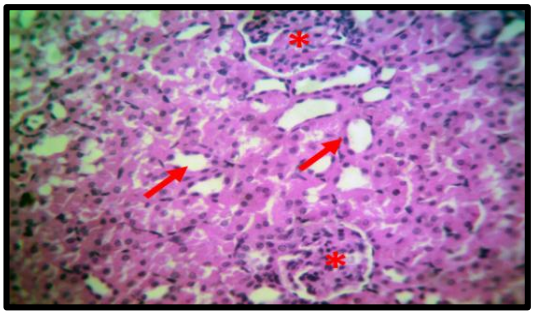

Fig. 4. Section of kidney from group B_1 showingnormal features. The glomeruli (*) and tubules (arrows) are normal. Stain: H&E. Magnification: X100

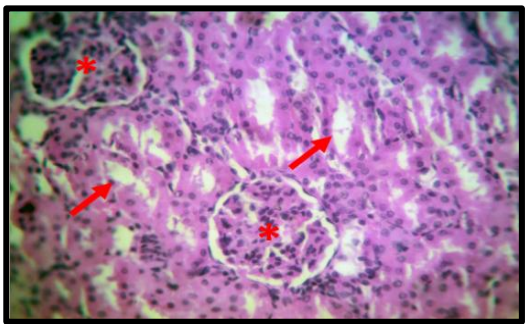

Fig. 5. Section of kidney from group B_2 showing normal features. The glomeruli (*) and tubules (arrows) are normal. Stain: H&E. Magnification: X100

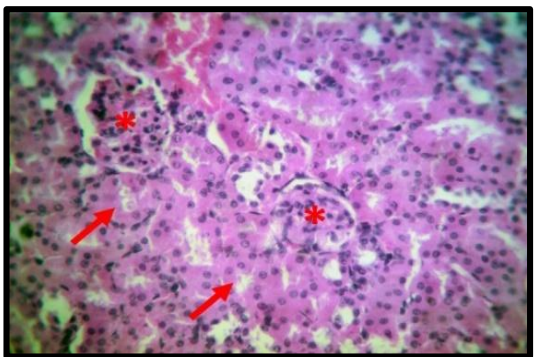

Fig. 6. Section of kidney from group B_3 showing normal features. The glomeruli (*) and tubules (arrows)are normal. Stain: H&E. Magnification: X100

3.2 Relative Organ Weights (Index)

Table 1: shows that the mean kidney weight index of treatment groups and control were not significant. Therefore, no changes were observed in extract treatment groups when compared with the control.

3.3 Serum Biochemical Parameters

Albumin level in group B shows significant increase $P<0.05$ when compared with treated group B_2 and B_3. Urea and creatinine show no evidence of statistically significant in all the groups.

3.4 Kidney Section

Group B kidney section shows a constricted glomerulus and some renal tubules containing eosinophilic cast while liver sections from group B_1 B_2, B_3 shows normal histoarchitecture, glomeruli and tubules.

3.5 Kidney Sections of Curative Effect Groups

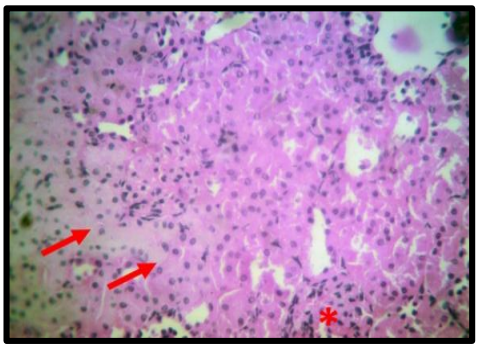

Fig. 7. Section of kidney from group BA_1 showing degenerative changes. The glomeruli (*) are enlarged with increased cellularity and some tubules show degenerative changes characterized by increased eosinophilia (arrows). Stain: H&E. Magnification: X100

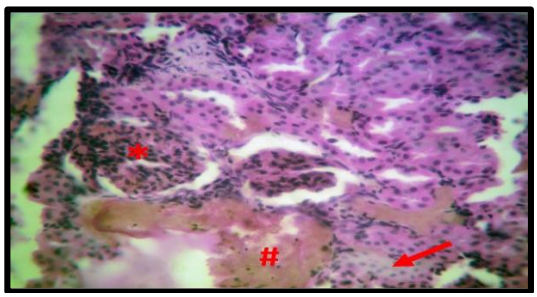

Fig. 8. Section of kidney from group BA_2 showing degenerative changes. The glomeruli (*) appear normal and tubules show degenerative changes characterized by increased eosinophilia (arrows) while some have undergone necrosis (#). Stain: H&E. Magnification: X100

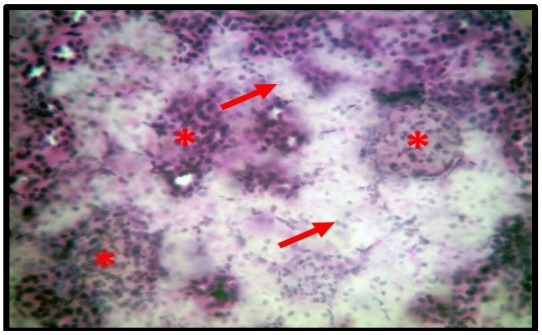

Fig. 9. Section of kidney from group BA_3 showing degenerative changes. The glomeruli (*) are enlarged with increased cellularity and tubules show degenerative changes characterized by increased eosinophilia (arrows) while some have undergone necrosis (#). Stain: H&E. Magnification: X100

3.6 Curative Effect against Ibuprofen Toxicity

3.6.1 Relative organ weights (Index)

Shows significance decrease in kidney organ weight when compared with BA_2 where no significance changes were observed among other groups.

3.6.2 Serum biochemical parameters

Group B showed significant decrease in urea, creatinine and Albumin when compared with treated groups BA_2 BA_3; BA_1 BA_2 BA_3; BA_1 BA_2 BA_3; respectively. BA_1 showed significance decrease effect in urea when compared with other treatment group BA_2, BA_3 while group BA_2, showed decreased in albumin when compared with BA_3.

3.6.3 Histopathological findings

Section of kidney from group BA_1 shows degenerative changes. The glomeruli are enlarged with increased cellularity and some tubules degenerative changes characterized by increased eosinophilia. Section of kidney from group BA_2 shows normal glomeruli and tubules with degenerative changes characterized by increased eosinophilia while some have undergone necrosis. Kidney section from group BA_3 show enlarged glomeruli with increased cellularity and tubules showing degenerative changes characterized by increased eosinophilia while some have undergone necrosis.

Ibuprofen is a Non-steroidal anti-inflammatory drugs (NSAIDs) non- selective cyloxynase inhibitory effect on prostaglandin synthesis mainly prostacyclins (PGE_2 and PGD_2) [11]. NSAID abusive action on cyclooxygenase (COX) enzyme inhibited interfering on arachidonic acid conversion into C_2 prostaglandins, prostacyclins and thromboxanes causing acute kidney damage, interstitial nephritis and chronic kidney damage [12]. In the test statistic to determine relative organ weight of rats treated with

Table 1. Relative Organ Weights (Index) Ibuprofen protective treatment

	GROUPS							
ORGAN	**B_0**	**B_X**	**B_S**	**B**	**B_1**	**B_2**	**B_3**	**B_2**
KIDNEY	0.69± 0.04	0.64± 0.01	0.69± 0.01	0.75± 0.02	0.70± 0.02	0.73± 0.01	0.74± 0.01	0.73± 0.01

*Values expressed as mean ± S.E.M. Statistical significance was set a P < 0.05. * - P < 0.05 compared to the corresponding group in superscript*

Table 2. Biochemical Parameters Ibuprofenprotective treatmentagainst Ibuprofen Groups

Parameters	**B_0(Negative Control)**	**B_X**	**B_S**	**B_1**	**B_2**	**B_3**
Urea	3.63 ± 0.09	3.33 ± 0.18	4.43 ± 0.43	3.67 ± 0.03	3.13 ± 0.03	3.27 ± 0.09
Creatinine	39.37 ± 1.43	62.07 ± 2.85	58.47 ± 6.25	54.10 ± 2.37	58.83 ± 1.18	54.87 ± 2.72
Albumin	29.03 ± 0.86	40.60 ± 0.56	39.03 ± 0.77	34.03 ± 0.81	45.37± $1.43^{**\ B}$	40.43 ± $0.99^{**\ B}$

*Values expressed as mean ± S.E.M. Statistical significance was set a P < 0.05. * - P < 0.05 while ** - P < 0.001 compared to corresponding group in superscript*

Table 3. Relative organ weights (Index) curative effect

	Groups			
ORGAN	**B**	**BA_1**	**BA_2**	**BA_3**
KIDNEY	0.75 ± 0.02	0.82 ± 0.01	0.75 ± 0.01^{*BA_1}	0.79 ± 0.01

*Values expressed as mean ± S.E.M. Statistical significance was set a P < 0.05. * - P < 0.05 compared to corresponding group in superscript*

Table 4. Biochemical Parameters of curative effect

	GROUPS			
	B	**BA_1**	**BA_2**	**BA_3**
UREA	3.63 ± 0.09	3.93 ± 0.09	6.17 ± 0.35$^{**B, BA_1}$	6.70 ± 0.26$^{**B, BA_1}$
CREATININE	39.37 ± 1.43	67.80 ± 2.06$^{** B}$	65.40 ± 1.30$^{** B}$	81.53 ± 9.85$^{** B}$
ALBUMIN	29.03 ± 0.86	44.43 ± 1.98$^{** B}$	42.97 ± 1.43$^{** B}$	32.93 ± 1.95$^{** B,BA_2}$

*Values expressed as mean ± S.E.M. Statistical significance was set a P < 0.05. * - P < 0.05 while ** - P < 0.001 compared to corresponding group in superscript*

ibuprofen and ethanol stem bark extract of the plant, no significant increase in kidney organ weights were observed in protective treatment groups. However, there is elevation in parameters of all the treated groups when compared with the untreated group.

4. CONCLUSION

The study indicates degenerative changes in the kidney of the untreated rats upon microscopic examination (B group). From the study, the extract treatments inhibited ibuprofen induced nephrotoxicity.

ETHICAL APPROVAL

Animal Ethic committee approval has been taken to carry out this study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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