Hepatorenal indices of toxicity in rats treated with aqueous *Khaya senegalensis* stem bark extract

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ABSTRACT

Background: Therapeutic use of plant materials is not without toxic impacts on metabolic and excretory processes in the body.

Objective: This study investigated toxicological impacts of *Khaya senegalensis* stem bark using plasma levels of hepatic and renal dysfunction biomarkers.

Methods: Forty (40) Wistar rats divided into five equal groups (n=8) was administered with distil water (control) and graded doses of aqueous *Khaya senegalensis* stem bark extract (test) for eight weeks. Blood was collected to determine aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), total protein, albumin, urea, creatinine and bilirubin (total and conjugated) levels. Liver and kidneys were harvested for histological studies.

Results: A significant increase ($p<0.05$) in AST, ALT, ALP, urea, creatinine, total bilirubin, chloride and bicarbonate levels and a significant decrease ($p<0.05$) in total protein, albumin, globulin and conjugated bilirubin level was observed. Liver photomicrograph revealed prominent nuclei, kupffer cells, glycogen accumulation and nuclei fragments within the hepatocytes. Kidney photomicrograph showed poorly aligned podocytes within the glomerulus and Bowman capsule, increased capsular space, proximal and distal convoluted tubules with poorly outlined epithelia, and thinned-out appearances of Bowman's capsule epithelium.

Conclusion: Repeated administration of aqueous *Khaya senegalensis* stem bark extract is toxic to the liver and kidneys in a dose-dependent manner.

Keywords: *Khaya senegalensis,* biochemical parameters, electrolytes, kidneys, liver,

Indices hépatorénaux de toxicité chez les rats traités avec un extrait aqueux d'écorce de tige de *Khaya senegalensis*

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RÉSUMÉ

Contexte: L'utilisation thérapeutique de matières végétales n'est pas sans effets toxiques sur les processus métaboliques et excrétoires de l'organisme.

Objectif: Cette étude a examiné les effets toxicologiques de l'écorce de tige de *Khaya senegalensis* en mesurant les niveaux plasmatiques de biomarqueurs de dysfonctionnement hépatique et rénal.

Méthodes: Quarante (40) rats Wistar répartis en cinq groupes égaux (n = 8) ont reçu de l'eau distillée (témoin) et des doses graduées d'extrait aqueux d'écorce de tige de *Khaya senegalensis* (test) pendant huit semaines. Des prélèvements sanguins ont été effectués pour déterminer les taux d'aspartate transaminase (AST), d'alanine transaminase (ALT), de phosphatase alcaline (ALP), de protéines totales, d'albumine, d'urée, de créatinine et de bilirubine (totale et conjuguée). Le foie et les reins ont été prélevés pour des études histologiques.

Résultats: Une augmentation significative ($p<0,05$) des taux d'AST, d'ALT, d'ALP, d'urée, de créatinine, de bilirubine totale, de chlorure et de bicarbonate et une diminution significative ($p<0,05$) des taux de protéines totales, d'albumine, de globuline et de bilirubine conjuguée ont été observées. La photomicrographie du foie a révélé des noyaux proéminents, des cellules de Kupffer, une accumulation de glycogène et des fragments de noyaux dans les hépatocytes. La photomicrographie du rein a montré des podocytes mal alignés dans le glomérule et la capsule de Bowman, un espace capsulaire accru, des tubules contournés proximaux et distaux avec des épithéliums mal délimités et un amincissement de l'épithélium de la capsule de Bowman.

Conclusion: L'administration répétée d'extrait aqueux d'écorce de tige de *Khaya senegalensis* est toxique pour le foie et les reins de manière dose-dépendante.

Mots clés: Khaya senegalensis, paramètres biochimiques, électrolytes, reins, foie,

INTRODUCTION

Toxicological evaluation of plant materials is usually done to establish safety of their consumption and predict their effects on human systems. For most toxicological studies animal models, especially mice and rats, are generally used before extrapolations or clinical trials in human being. Results obtained from such toxicological studies are considered together with the vehicle of administration, as this may be the avenue for any observed toxicological signs and not the plant materials.

Adverse effects of orally administered substances varies ranging from acute effects to chronic effects. While acute toxicity from ingestion of a plant material refers to the adverse unbearable effects that occurs following ingestion of a single dose or multiple doses of such plant materials within a period of twenty four hours, chronic toxicity, on the other hand, can occur when such plant is ingested beyond twenty four hour period.[1,2] The liver is known to be the main target organ by toxic substances in ingested xenobiotics, due to how almost all digested substances go through it for bioactivation or detoxification.[3,4] The kidneys, on the other hand, filters waste products generated following ingestion of such substances out of blood, making it a vulnerable organ for toxicological impact of metabolites from such xenobiotics.[5,6]

Management approach to diseases varies but rather include preventive and definitive methods which involves the use of drugs or surgical intervention. The therapeutic use of drugs is not without its short comings ranging from availability, efficacy, and side effects to cost implications, especially amongst people in low-income countries who are living with chronic diseases that requires life-long drug dependence. In such situations, people look for alternatives which include searching for active phytochemicals in plant parts (leaves, stem bark, roots, fruits, seeds, and flowers) to serve as readily available cost-friendly but effective alternatives to existing expensive drugs and therapeutic interventions for diseases that had evaded therapeutic dose ranges of available medicines.

Discovery of drugs for such therapeutic purposes involves pre-clinical researches during which rigorous scientific investigations and evaluations are carried out to identify potential drugs and their biological targets, and ensure their efficacy and safety potentials before clinical trials. However, *Khaya senegalensis* stem bark has been anecdotally used in traditional medicine for the treatment of ailments and alleviation of clinical conditions in many diseases including malaria, bacterial infection, parasitic infection, diabetes mellitus, sickle cell disease, and jaundice, due to its antimalarial, antimicrobial, anthelmintic, antioxidant, anti-inflammatory, antihyperglycemic, and antisickling properties.[7,8] While some of the phytochemicals present in this plant material are naturally safe with little or no toxicological implication, some are very toxic, causing dysfunctions especially in organs of metabolic and excretory importance. The toxicity in this instance might be relative, as determined by many factors including the doses, route of administration, duration of use, presence of active metabolites, oxidative status, immunological responses, nutritional status, and pre-administration conditions of the liver and kidneys. This study, therefore, investigated the toxicological impact of aqueous *Khaya senegalensis* stem bark extract in Wistar rats using plasma levels of hepatic and renal indices of toxicity.

MATERIALS AND METHODS

Plant materials

Khaya senegalensis stem bark was gotten from a garden at the Federal University of Agriculture, Abeokuta, identified and authenticated by a taxonomist in the Department of Forestry and Wildlife Management, and given a herbarium identity number (UAHA/017/004/0001). The *Khaya senegalensis* stem bark was cut into small pieces, pulverised into fine powder using a grinding machine.

Aqueous extraction/maceration

About 4 kg of powdered *Khaya senegalensis* stem bark was added to 12 L of water in an air-tight plastic container at room temperature (22 - 28^{o}C) for seven days with frequent shaking. The obtained solution was decanted, filtered and then concentrated using rotary evaporator, giving a yield of 81.2%. The concentrate was subsequently dried and stored at room temperature.

Study design

This is a sub-chronic longitudinal study that was carried out using a total of 40 non-gravid female adult Wistar strain Albino rats (weight range 200 - 250 g) obtained from Anatomy Department, University of Ibadan. The rats were randomly divided into five different groups (I-V), each consisting of eight rats as follows:

Group 1: Fed with normal rat chow and 2 mL distilled water.

Group 2: Fed with normal rat chow and 50 mg/kg body weight (bw) *Khaya senegalensis* stem bark extract.

Group 3: Fed with normal rat chow and 100 mg/kg bw *Khaya senegalensis* stem bark extract.
Group 4: Fed with normal rat chow and 150 mg/kg bw *Khaya senegalensis* stem bark extract.
Group 5: Fed with normal rat chow and 200 mg/kg bw *Khaya senegalensis* stem bark extract.

Dosing of rats with *Khaya senegalensis* stem bark extract

The aqueous *Khaya senegalensis stem* bark extracts and water were administered orally and daily for eight weeks (56 days). The doses used were 50 mg/kg, 100 mg/kg, 150 mg/kg, and 200 mg/kg. Each dose was freshly prepared and administered orally daily, as a single dose, for a period of eight weeks through oral cannula.

Care of animals

The rats were taken care of using the US Public Health Service Guidelines.[9] Factors that affects animal well-being, including space, light, noise, and temperature, were taken care of. Cages were made of non-toxic plastic materials and smooth surfaced; designed to prevent animal escape and allowed for cleaning, disinfecting and regular animal handling; prevent accidental entrapment of animals and free of projections that may injure the rats. The animal house is well-ventilated, relatively silent from noise, maintained at a room temperature of 22-28°C and under the natural cycle of daylight and night darkness.

Blood sample and organ collection

At the expiration of eight weeks (56 days), the rats were fasted overnight and blood samples were collected by cardiac puncture, under diethyl ether anaesthesia, into lithium heparin and ethylene diamine tetracetic acid (EDTA) specimen bottles for biochemical and haematological analysis respectively.

The collected bloods were centrifuged at 5000 rpm for 5 minutes to obtain the plasma, which was separated into plain bottles and kept at -20°C till analysed. Also, the liver and kidneys were harvested and suspended in 10% formol saline till fixed for histological studies.

Biochemical studies

This was performed using hepatic and renal biomarkers of toxicity, as these are the major organs for regulation of metabolism and waste excretion. Plasma aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) enzyme activities; total protein; albumin; urea; creatinine; and bilirubin (total and conjugated) concentrations were determined using standard methods.[10-17] Plasma globulin was determined as difference between total protein and albumin concentrations (Globulin = Total protein - Albumin).

Slide preparation and histological studies

Liver and kidney tissues were fixed in formol saline. The tissues were sliced (not exceeding 5 mm), labelled, further fixed for 24 h, and processed using automatic tissue processor (Histokinette) with the eighteen hours schedules. The tissues were embedded, allowed to solidify and the tissue blocks removed.[18] Tissue blocks were trimmed (to remove excess wax), cut into serial section at 4 µ and floated out on water bath at 50°C using floating slides and 20 % alcohol. The tissue sections were picked with a clean grease-free albuminized slide, cleaned, labelled with a diamond pencil, and dried on hot plate for 30 minutes. Tissue slides were stained with Mayer's haematoxylin and eosin, mounted on microscope, and examined using oil immersion objective lens (x 100).

Statistical analysis

Data obtained was analysed using SPSS version 25. Variables were expressed as Mean and standard error of mean (Mean ± SEM) and levels of statistical significance was set at $p < 0.05$. Mean differences between the groups were compared using one way ANOVA.

RESULTS

Hepatorenal markers of aqueous *Khaya senegalensis* extract toxicity

Result of biomarkers of liver and kidneys toxicity revealed a significant increase ($p < 0.05$) in plasma AST, ALT, and ALP activities ; and plasma urea and creatinine concentrations in all the administered doses of aqueous *Khaya senegalensis* stem bark extract treated rats in comparison to control in a dose-dependent manner (Table 1).

Effect of *Khaya senegalensis* extract on plasma biochemical parameters

Result of plasma biochemical parameters showed a significant decrease ($p < 0.05$) in total protein, albumin, and globulin levels in groups fed on various doses of aqueous *Khaya senegalensis* stem bark extract in comparison to the control group (Table 2). Also, a significant increase ($p < 0.05$) in plasma total bilirubin and a significant decrease ($p < 0.05$) in plasma conjugated bilirubin concentrations among rats administered with different doses of aqueous *Khaya senegalensis* stem bark extract (Table 2).

Effect of *Khaya Senegalensis* extract on plasma

electrolytes

Result from this study showed a significant increase ($p < 0.05$) in plasma chloride and bicarbonate levels and a non-significant increase ($p > 0.05$) in plasma sodium and potassium concentrations among rats administered with different doses of aqueous *Khaya senegalensis* stem bark extract (Table 3)

Effect of *Khaya senegalensis* extract on liver photomicrograph

Liver photomicrograph revealed normal histology of hepatocytes with visible nuclei, sinusoids, few Kupffer cells, and little glycogen accumulation in control rats (Figure 1). Amongst the test group, liver photomicrograph showed hepatocytes with prominent nuclei; presence of kupfer cells and RBCs within the central vein; glycogen accumulation with some hepatocytes appearing pale; nuclei fragments (nuclear inclusions) and congestion of cells within the liver tissue in groups dosed with 50, 100, 150, and 200 mg/kg of *Khaya Senegalensis* stem bark extract respectively (Figure 1)

Effect of *Khaya senegalensis* extract on kidney photomicrograph

Result of kidneys photomicrograph showed normal histology of glomerulus, podocytes, capsular space, with distal and proximal convoluted tubules having well outlined epithelium in the control rats. However, in rats dosed with aqueous *Khaya senegalensis* stem bark extract, the glomerulus appeared altered, with poorly aligned podocytes present within the glomerulus and Bowman capsule but the distal convoluted tubule is well aligned. Also, there is increased capsular space, poorly outlined epithelium of the proximal and distal convoluted tubules, congestion of proximal convoluted lumen; and thinned-out appearance of Bowman's capsule epithelium (Figure 2).

Table 1: Plasma hepatorenal markers of aqueous *Khaya senegalensis* extract toxicity

Parameters	Group A Water	Group B 50mg/kg	Group C 100mg/kg	Group D 150mg/kg	Group E 200mg/kg	F	P value
Aspartate transaminase (IU/L)	44.00±2.66	53.00±1.24*	55.67±2.13*	57.50±1.71*	57.60±1.88*	11.268	0.001
Alanine transaminase (IU/L)	39.00±41.01	44.00±1.39*	44.67±15.70*	46.00±1.41*	52.00±14.14*	21.071	0.001
Alkaline phosphatase (IU/L)	22.00±2.83	41.50±0.71	46.67±6.11	58.00±33.94	69.00±4.24	4.831	0.001*
Urea (mg/dl)	16.64±0.83	18.10±9.96	24.75±15.28*	26.64±0.83*	27.03±11.29*	8.42	0.000
Creatinine (mg/dl)	0.95±0.07	1.04±0.07*	1.07±0.15*	1.25±0.28*	1.35±0.07*	56.82	0.002

Values are Mean ± Standard error of mean (SEM) and statistically significant (*) at $p < 0.05$.

Table 2: Plasma biochemical parameters among *Khaya Senegalensis* extract treated and control rats.

Parameters	Group A Water	Group B 50mg/kg	Group C 100 mg/kg	Group D 150mg/kg	Group E 200mg/kg	F	P value
Total protein (g/L)	9.45±0.64	8.40±0.85	8.20±0.30	8.05±0.08	7.60±0.28	4.69	0.381
Albumin (g/L)	4.95±0.14	4.20±0.14	4.10±0.10	4.00±0.07	4.05±0.28	0.89	0.090
Globulin (g/L)	4.50±0.78	4.20±0.28	4.10±1.27	4.05±0.07	3.55±0.00	2.560	0.570
Total bilirubin (mg/dL)	1.20±0.28	1.45±0.07	1.67±0.12	2.60±0.00	2.70±0.14	4.940	0.001*
Conjugated bilirubin (mg/dL)	0.50±0.14	0.35±0.07	0.33±0.12	0.30±0.14	0.40±0.14	4.644	0.001*

Values are Mean ± Standard error of mean (SEM) and statistically significant (*) at $p < 0.05$.

Table 3: Plasma electrolytes among aqueous *Khaya senegalensis* stem bark extract treated rats and control group.

Parameters	Group A Water	Group B 50mg/kg	Group C 100 mg/kg	Group D 150mg/kg	Group E 200mg/kg	F	P value
Na^+(mmol/L)	128.82±0.58	129.22±0.14	129.23±2.56	130.61±3.68	132.97±3.96	149.791	0.581
K^+ (mmol/L)	7.00±2.12	7.85±0.07	8.16±0.64	8.39±1.24	9.23±2.52	18.790	0.410
Cl^- (mmol/L)	95.24±1.42	95.31±0.07	95.69±5.02	96.04±1.39	97.24±1.27	126.982	0.001
HCO_3 (mmol/L)	6.10±1.98	6.70±0.28	8.50±0.14	8.60±4.67	8.77±6.92	6.161	0.001

Values are mean ± standard deviation, * statistically significant (*) at $p < 0.05$, where Na^+ = Sodium, K^+ = Potassium, Cl^- = Chloride, and HCO_3^- = Bicarbonate

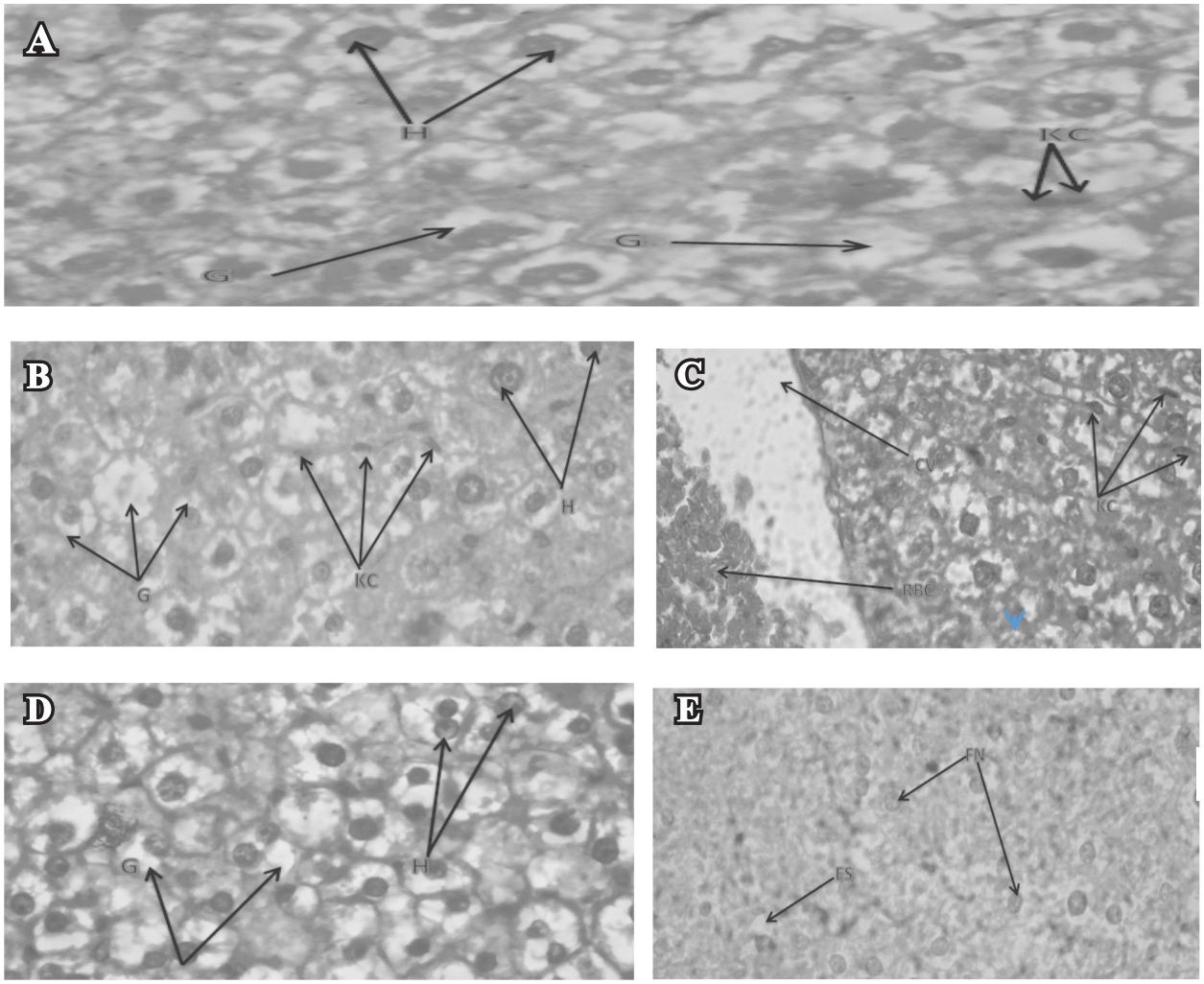

Figure 1: Liver photomicrographs of control and *Khaya senegalensis* treated rats (Mag x400).

Where A = Control, B = 50mg/kg, C = 100mg/kg, D = 150mg/kg, E = 200mg/kg

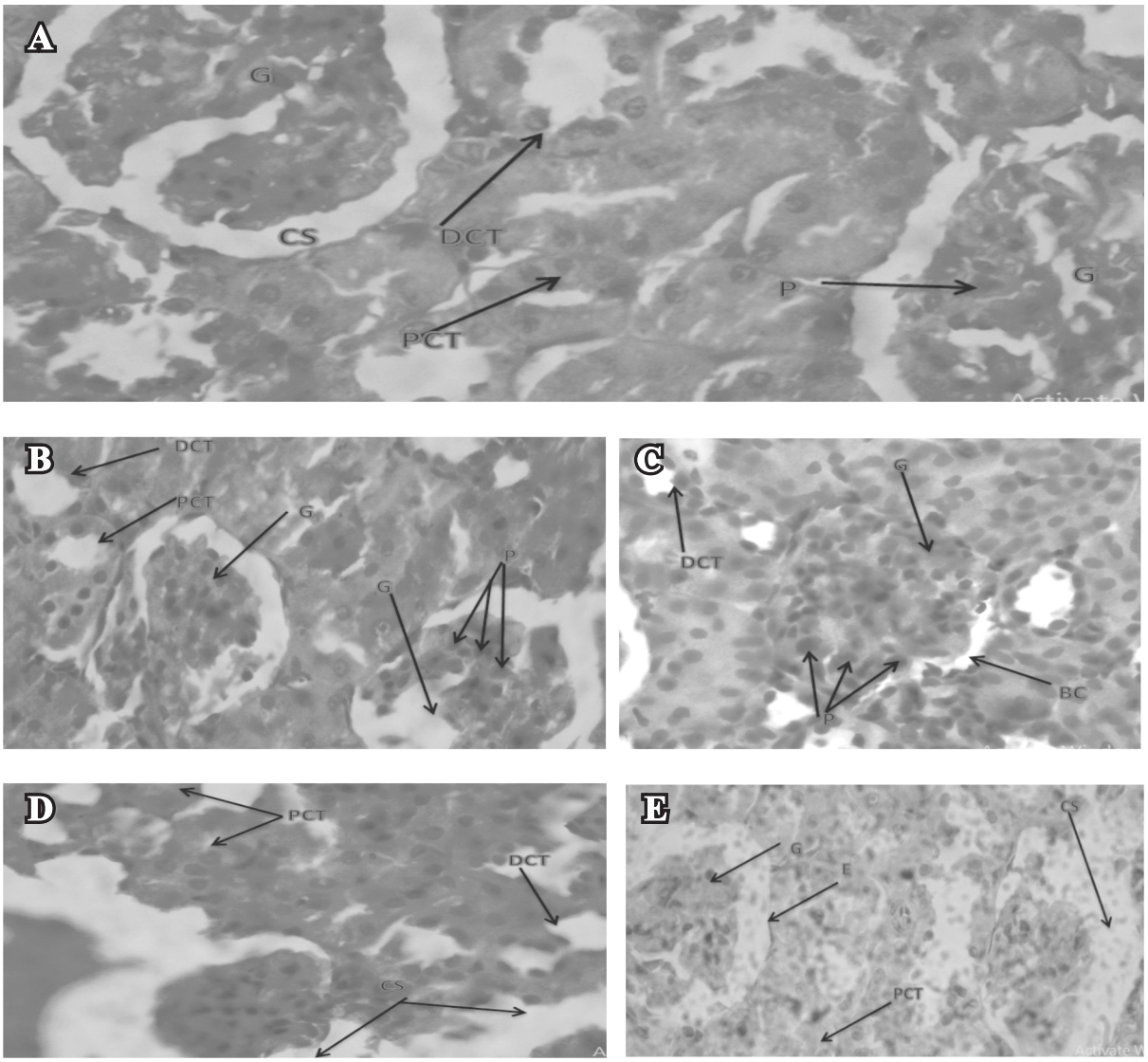

Figure 2: Kidney photomicrographs of control and *Khaya senegalensis* treated rats (Mag x400).

Where A = Control, B = 50mg/kg, C = 100mg/kg, D = 150mg/kg, E = 200mg/kg

DISCUSSION

Well-established biomarkers generally used to analyse the pathophysiological state of the liver and kidneys include AST, ALT, ALP activities; and plasma urea and creatinine levels. Result from this study revealed a significant increase ($p < 0.05$) in plasma AST, ALT, and ALP activities across the table in a dose-dependent manner in all the aqueous *Khaya senegalensis* stem bark extract treated rats in comparison to control (Table 1). This finding corroborates earlier reported raised plasma AST and ALT activities in rats and rabbits fed with *Khaya senegalensis* extract.[19,20] This indicate that *Khaya senegalensis* stem bark extract harmfully affect liver functions.

Both AST and ALT are biomarkers of liver toxicity with ALT being a more specific marker of hepatocellular integrity measures. The observed increase in plasma transaminases (AST and ALI) activities in this study suggests the release of these enzymes from liver cytosol into blood circulation. However, due to non-liver specificity of AST, the high plasma level may be from diseases of the heart, muscle, kidney, brain, and red blood cells where this enzyme is also synthesised. [21]

Alkaline phosphatase enzyme activity is often employed to assess the liver function, patency of bile duct and integrity of hepatocyte plasma membrane. The observed raised plasma ALP activities after administration of aqueous *Khaya senegalensis* stem bark implies disruption of hepatocytes plasma membrane or induction of osteoblasts by the extract for physiological bone growth

or compensatory bone growth during necrotic changes in bones.[22] Thus, the observed increased activities of ALP in rats administered with various doses of aqueous *Khaya senegalensis* stem bark extract might not specifically indicate hepatotoxic effect of the extracts but may indicate changes occurring in other tissues or organs where ALP is produced.

High plasma urea and creatinine levels are considered significant markers of renal dysfunction. Considering plasma level of renal dysfunction markers, a significant increase ($p < 0.05$) in plasma urea and creatinine concentrations was observed among rats administered with different doses of aqueous *Khaya senegalensis* stem bark extract, in a dose-dependent manner (Table 1). These results agrees with findings from similar studies by Onu *et al*.[19] and Kolawole *et al*.[23] who reported high plasma urea and creatinine in *Khaya senegalensis* stem bark extract fed rats. The observed increase in plasma urea and creatinine is suggestive of defective kidney excretory functions due to extract-induced acute kidney injury. However, since the level of urea is not considered a complete measure of renal function, the observed increase in creatinine could reinforce the claim that the extract is nephrotoxic.

Considering biochemical parameters, a significant decrease ($p < 0.05$) in plasma total protein, albumin, and globulin was observed in groups fed on various doses of aqueous *Khaya Senegalensis* stem bark extract in comparison to the control group (Table 2). This finding corroborated report from similar study by Onu *et al.*[19] but contrast that of Kolawole *et al*.[23], who reported high total protein concentration in serum of rats fed on aqueous *Khaya senegalensis* stem bark extract. The observed decrease in total protein and albumin is an indication of affectation of the synthetic functions of liver and increased excretion of protein by the kidneys. The plasma total protein and albumin levels thus reflect extent of damage to the liver and kidneys by the administered extract. However, the observed hyperglobulinemia amongst extract-treated rats may suggest an on-going inflammatory processes or infection in the rats.

Blood bilirubin is a product of haemoglobin breakdown, with the liver playing important roles in converting bilirubin from a lipophilic molecule to a hydrophilic molecule for easy excretion.

The conjugating, molecule binding, excreting, and synthetic abilities of hepatocytes' are usually indirectly measured using blood bilirubin level. Result obtained from this study revealed a significant increase ($p < 0.05$) in plasma total bilirubin concentration and a significant decrease ($p < 0.05$) in plasma conjugated bilirubin concentration among rats administered with different doses of aqueous Khaya senegalensis stem bark extract (Table 2). This finding corroborates that of Onu *et al*.[19] and Abubakar *et al.*[24] The observed increase in plasma total bilirubin concentration may indicate increase rate of production and release of bilirubin into the plasma as occurs in cases of haemolysis due to disruption of RBC membrane integrity. Thus, the administered aqueous extracts may damage the RBC membrane resulting in the observed hyperbilirubinemia. On the other hand, the observed decrease in plasma conjugated bilirubin concentration may indicate competitive inhibition of unconjugated bilirubin binding to albumin; displacement of bound unconjugated bilirubin from albumin; inhibition of hepatic uptake of bound unconjugated bilirubin; competitive prevention of binding of unconjugated bilirubin to ligandin Y (a cytoplasmic protein that transport unconjugated bilirubin to the smooth endoplasmic reticulum) or inhibition of UDP-glucuronyl transferase enzyme responsible for the conjugation of bilirubin by a component of the plant extracts. All these are indications of reduced ability of the liver to conjugate bilirubin, implying hepatotoxic effect of the extract.

The importance of the kidneys in regulating blood volume, blood pressure, blood electrolytes, acid-base balances and osmolarity of the extracellular fluid within narrow limits is dependent on their ability to maintain filtration, reabsorption, and secretion processes. Blood electrolyte homeostasis involves increasing electrolyte reabsorption whenever concentration is low and increasing their secretion and excretion when concentration is in excess. Result from this study showed a significant increase ($p < 0.05$) in plasma chloride and bicarbonate levels and a non-significant increase ($p > 0.05$) in plasma sodium and potassium concentrations among rats administered with different doses of aqueous *Khaya senegalensis* stem bark extract (Table 3). This agrees with the earlier reported increase in these electrolytes in rats fed with aqueous *Khaya senegalensis* stem bark extract.[23] These observations indicate affectation of osmo-regulatory functions of the kidneys and confirms association of some degrees of renal dysfunction with *Khaya senegalensis* stem bark extract ingestion.

The liver, as a detoxifying organ, is exposed to various

toxicological insults making it to undergo necrotic changes, cellular degeneration, bile duct hyperplasia and fibrosis.[25] From this study, the liver photomicrographs revealed normal histology of hepatocytes with visible nuclei, sinusoids, few Kupffer cells, and little glycogen accumulation in control rats. Amongst the test group administered with aqueous *Khaya senegalensis* stem bark extract, liver photomicrograph showed hepatocytes with prominent nuclei; presence of kupffer cells and RBCs within the central vein; glycogen accumulation with some hepatocytes appearing pale; nuclei fragments (nuclear inclusions) and congestion of cells within the liver tissue in groups dosed with 50, 100, 150, and 200 mg/kg of Khaya Senegalensis stem bark extract respectively (Figure 1). The observed hypochromic appearance, glycogen accumulations and nuclei fragments of hepatocytes among groups administered with different doses (especially at 200 mg/kg) of aqueous *Khaya senegalensis* stem bark extract, indicating disruption or loss of hepatocellular integrity. The presence of kupffer cells may indicate normal liver function and immune activity. However, when kupffer cells are in excess, it indicate liver diseases knowing that Kupffer cells plays important roles in detoxification, immune responses, and liver regeneration after injury by releasing signalling molecules that promote hepatocyte regeneration. Activation of kupffer cells can contribute to liver injury, inflammation, and fibrosis.[26,27] The observed glycogen accumulations in hepatocytes suggest glycogenic hepatopathy[28,29], observation of nuclei fragments (nuclear inclusions) in the hepatocytes indicate liver disease, the observed cell congestion in the liver tissue indicate impairment of blood flow and potential damage to liver tissue leading to inflammation and fibrosis. The cell congestion may be associated with hepatic venous outflow obstruction from compressive effect of the intrahepatic glycogen accumulation. These histological findings corroborates the observed significant increase in the concentration of liver toxicity biomarkers (AST, ALT, and ALP) in the plasma of such groups.

Photomicrograph of the kidneys showed normal histology of glomerulus, podocytes, capsular space, with distal and proximal convoluted tubules having well outlined epithelium in the control rats. Amongst rats dosed with aqueous *Khaya senegalensis* stem bark extract, the glomerulus appeared altered, with poorly aligned podocytes present within the glomerulus and Bowman capsule but the distal convoluted tubule is well aligned. Also, there is increased capsular space, poorly outlined epithelium of the proximal and distal convoluted tubules, congestion of proximal convoluted lumen; and thinned-out appearance of Bowman's capsule epithelium (Figure 2). The administered extract thus induces inflammatory responses and some degree of hardening and scarring of glomerulus thereby disrupting glomerular filtration, causing increased filtration pressure, increased capsular space, fluid accumulation in the Bowman's space and glomerular damage. The thinned-out appearances of Bowman's capsule epithelium implies affectation of selective permeability of the basement membrane and excretion capacity of the kidneys by the administered extract, through damage to the glomerular filtration barrier. These features corroborates the observed significant increase in the concentrations of biomarkers of renal toxicity (urea, creatinine) in the plasma of such groups and confirms the nephrotoxic effect of the administered aqueous *Khaya senegalensis* stem bark extract.

CONCLUSION

Findings based on the results from this study revealed that repeated administration of aqueous K*haya senegalensis* stem bark extract is both hepatotoxic and nephrotoxic in a dose-dependent manner. Thus, whenever it is required for any therapeutic purpose, it is suggested that low doses should be considered for the shortest possible period.

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