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Research Article

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Investigation of hepatorenal protection by aqueous extract of *Rhizophora racemosa* stem bark against Aspirin-induced toxicity in Wistar rats

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Abstract Aqueous extract of *Rhizophora racemosa* bark extract was investigated for liver and kidney protective properties following aspirin-induced toxicity. Sixteen (16) Wistar Albino rats weighing between 150g and 180g were divided into four (4) groups of four (4) rats each and were administered pre-treatment for fourteen (14) days as follows: group I (negative control) and group II (normal/positive control) received 0.2ml of normal saline each while group III and group IV received 400mg/kg (high dose of extract) and 200mg/kg (low dose of extract) respectively. On the fourteenth (14^{th}) day rats in groups II, III, and IV were administered 200mg/kg of Aspirin to induce liver and kidney toxicity. Four (4) hrs. Later all sixteen rats were sacrificed and blood was collected for assay of serum Aspartate transaminase, Alanine transaminase, Alkaline phosphatase, creatinine, and urea. The results indicate a significant ($p < 0.05$) increase in serum AST, ALP, ALT, creatinine, and urea while the extract restored them in a dose-dependent pattern significantly ($p < 0.05$) for AST and creatinine on a high dose and insignificantly for ($p > 0.05$) for ALP, ALT, and urea on a high dose. The results suggest that *Rhizophora racemosa* stem bark possesses hepatoprotective and nephroprotective properties.

Keywords *Rhizophora racemose,* Aspirin-induced toxicity

Introduction

Before the advent of chemical medicines/synthetic drugs/ pharmaceuticals man had depended largely on the healing/curative properties of various plants in the environment. A great percentage of the population of the world, especially of the developing countries, have relied on plants as an important/vital source of medication for diverse ailments (Enemchukwu et al, 2014).

Ethno-medicinal practitioners utilize virtually all parts of plants: bark, kernels, leaves, stem and roots for treatment of variety of ailments (Ainge and Brown, 2001). Because of their rich stock of phytochemicals various plants have provided protection, healing/treatment for diverse pathologies including not just hepato-renal protection but also accelerate liver and kidney healing processes. One of such plants is *Rhizophora racemosa.*

Rhizophora racemosa a species of the mangrove tree of the family *Rhizophoraceae,* is widely distributed along the Pacific coastline of Central and South America and of the Atlantic coast, estuaries, bays and lagoons of West Africa. Aside from economic uses such as for firewood/fuel and as construction poles, its uses medicinally are for stomach

ache, cramps, peptic and duodenal ulcer. *Rhizophora racemosa* stem bark extract has been credited with antibacterial properties arising particularly from the bioactivity of saponins, quinine and terpenoid (Ukoima et al, 2013).

Rhizophora racemosa was reported (Popp et al, 1984) to possess phytochemicals such as polysaccharides, triterpenes, tannins, carbohydrates, polyphenols, amino acids and waxes which are responsible for bleeding and wound burns. Pharmacological activities reported for mangroves are antioxidant, antimicrobial and antidiabetic. Because the plant presents with potential for an array of medicinal products and drug discovery, it is suggested to ensure due scientific diligencs to achieve safe and efficacious pharmacological products (Sadeer et al, 2019).

Because mangroves have exhibited potential as possible source for a wide variety medicinal products Sadeer *et al*, (2019) propose the need for careful research backed with proper scientific and clinical trials to guarantee safety and potent use of these plants and to verify their pharmacological properties and toxicity.

Commonly called Aspirin, acetylsalicylic acid (ASA) is anti-inflammatory drug. It is non-steroidal in nature and is employed against conditions such as headaches, various forms of arthritis, menstrual pain, toothaches, and joint and muscle pains arising from trauma amongst others (Drugs.com). New applications of aspirin are in the management of cardiovascular, pre-eclampsia, and cancer. Such wide application has greatly increased the number of persons exposed to aspirin, which is noted hemorrhagic effects (e.g., gastro-intestinal and intracranial bleedings (Dixit et al., 2008). Aspirin has recorded reactive oxygen species generation, coupled with altered oxidative stress biochemical markers in the liver and spleen of mice. (Bhattacharyya et al, 2014. Raza and John (2012) suggested increased aspirin-induced apoptosis through accelerated reactive oxygen species formation. Sebai et al (2014) report of oxidative stress presenting as increased malondialdehyde levels and a decline in levels of superoxide dismutase, catalase, and glutathione peroxidase activities. Aspirin is an irreversible inhibitor of the isoforms of cyclooxygenase: cyclooxygenase-1 (COX-1)/prostaglandin synthetase -1 (PTGS-1) and cyclooxygenase-2 (COX-2)/prostaglandin-2 (PTGS-2) (Sharma et al, 1997), though its selectivity is towards COX-1 9s Kerola and Vuolteenado, 2009). Its mechanism is through the acetylation of the serine residue – 529 (Vane and Botting, 2003) Cyclooxygenase produces prostaglandins which are proinflammatory and thromboxanes that promote clotting. Aspirin-modified COX-2 produces anti-inflammatory lipoxins.

Liver:

It weighs approximately 1500g, is the largest internal organ and is site for more than 500 vital metabolic functions (Naruse et al, 2007). Notable amongst its functions are gluconeogenesis, glycogenolysis, glycogenesis, breakdown of insulin and other hormones, protein metabolism (e.g., lactic acid conversion to alanine), synthesis of cholesterol, triglycerides (fats), production of various coagulation factors, protein C, protein S and anti-thrombin. Hemoglobin break-down by the liver produces bilirubin and biliverdin which are added to the bile. The liver also detoxifies harmful substances and breaks down drugs into less toxic and excretable forms, converts ammonia to urea, stores substances such as vitamin $B_{12,}$ iron, copper and glycogen. During very early pregnancy, the fetal liver starts production of red blood cell (RBC) up till the 32^{nd} week when the bone marrow takes over. The liver also produces albumin, the major osmolar component of blood serum. With such and much more, the functional health of the liver is clearly of great concern to Scientists and Health Practitioners in particular. Liver disease (hepatotoxicity or toxic hepatitis) is the distortion of liver function resulting in ill health. The critical nature of liver functions predisposes the body to ill health, when these functions are impaired or lost completely (Singh et al, 2011). In particular its role as the central clearing house (metabolism of exogenous compounds such as drugs and alcohol and transformation of chemicals) exposes the liver to toxic injury (Saukkonen et al, 2006).

The enzymes, Alkaline phosphatase, Alanine transaminase and Aspartate transaminase are markers of liver health status. The normal ranges for these enzymes are: AST 0 – 45IU/L; ALT 7 – 56IU/L and ALP 41 – 133IU/L (Diana 2007). Minor elevations in AST and ALT values associated with ALT/AST ratios > 1 indicate chronic viral hepatitis (HCV). Acute elevations with values toward 1000 are occasioned by acute viral hepatitis of such as Hepatitis A, Hepatitis E, Hepatitis B or even autoimmunity (Rahman 2007). Elevated ALP levels are indicative of hepatitis

presenting as cholestasis, hepatic and bony metastasis and cirrhosis (Rosalki and McIntyre, 1999. Low level of ALP is the result of hypothyroidism, pernicious anemia, zinc deficiency and congenital hypophosphatasia (Simko 1990).

Kidney:

The kidney is a complex organ responsible for a number of vital functions, notably, elimination of metabolic wastes: urea, creatinine and uric acid. The kidneys regulate extracellular fluid and plasma volume, acid-base balance, serum osmolality/blood pressure, homeostasis, electrolyte concentration and production of hormones such as erythropoietin, 1,25 dihydroxy vitamin D_3 and renin. Kidney function impairment presents with elevation of creatinine above the normal range of 0.6 -1.4mg/dL and 0.5 -1.2mg/dL for men and women respectively. Difference in the range for men and women is because women have less muscle than men. When kidney is unhealthy, blood urea level (Normal: 7-20mg/dL) shoots up, though such could also be the result of heart failure and dehydration.

Materials and Methods

Chemicals and reagents: The under-listed chemicals and reagents of analytical grade were used for this study. They include aspirin (Burgoyne Laboratory Reagents), chloroform (JDH), Aspartate Transaminase, Alanine Transaminase, Alkaline Phosphatase, Creatinine and Urea Biochemical kits (Randox Laboratories LTD).

Plant extract preparation: The stem of the plant, *Rizophora racemosa* was harvested from Edema in Ogbia Local Government Area, Bayelsa State, Nigeria, and left under shade to dry for two weeks following which it was processed into fine powder. Extract was prepared by soaking 500gm of plant powder in 2liters of distilled water for 48hrs with intermittent stirring. After filtration with filter paper (110mm Whatman), filtrate was evaporated in water bath at 40°C. The resultant residue was later reconstituted to suit the experimental design.

Animals and experimental design: Sixteen (16) male Albino Wistar rats weighing between 150-180g were purchased from the animal house of Department of Pharmacology, Faculty of Basic Medical Sciences, College of Health Sciences, Niger Delta University, Wilberforce Island, Bayelsa State, Nigeria and were acclimatized for a period of fourteen (14) days using standard plastic rat cages in the research laboratory of the same department. During the acclimatization and experiment were kept in pathogen free environment with access to clean water *ad libitum*, standard commercial grower's mash/rodent diet. Environment of the entire experiment was properly ventilated.

The animals were randomly grouped into four (4) groups of four (4) rats each treated as described below in procedure and treatment.

Procedure and treatment: The rats were fasted for 24 hours prior to commencement of the experiment but had access to clean drinking water. While animals in group I and group II were orally administered pretreatment with 0.2ml of distilled water with the aid of a gavage tube, animals in groups III and IV were administered 400mg/kg (high dose) and 200mg/kg (low dose respectively. On the fourteenth (14^{th}) day, one hour after their usual pretreatments, animals in groups II, III and IV were orally administered 200mg/kg of Aspirin to induce liver and kidney toxicity. Four (4) hours after aspirin 'poisoning', all the animals were sacrificed following anesthesia with chloroform. Thereafter blood was collected into plain bottles after cardiac puncture and allowed $1^1/_2$hrs to coagulate. Afterwards, blood samples were centrifuged at 2000 rpm for ten minutes and the serum was collected for analysis of liver and kidney toxicity/parameters.

Biochemical Assays

Estimation of serum alanine aminotransferase (ALT) was carried out according the principle prescribed by Reitman and Frankel (1957).

Serum aspartate aminotransferase (AST) estimation was carried out according the Reitman and Frankel (1957) method.

Serum alkaline phosphatase (ALP) was assayed spectrophotometrically according the King and Armstrong method (Buch and Buch 2009).

Serum creatinine was also estimated spectrophotometrically based on the Max Jaffe reaction. (Hawk et al, 1948).
Serum urea was estimation was premised on the Bertholet or indophenol reaction (Searle 1984).
Results obtained were subjected to statistical Analysis of Variance (ANOVA) and are presented below.

Results

The results for the investigation of the effect of aqueous extract of *Rhizophora racemosa* stem bark on the AST, ALT, ALP, creatinine, and urea profiles of aspirin-induced liver and kidney toxicity in Wistar albino rats are presented below:

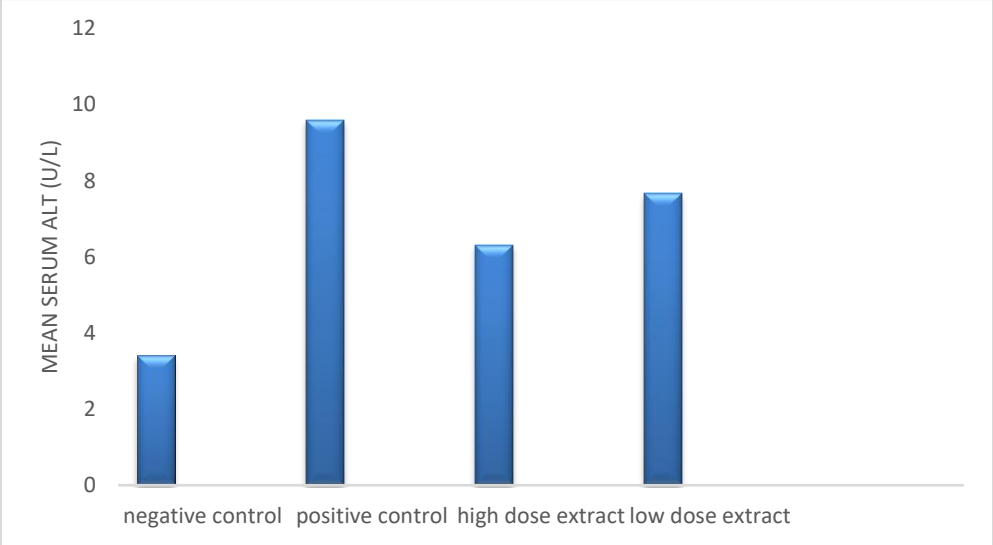

Figure 1: The effect of aqueous extract of Rhizophora racemosa stem bark on serum ALT

Results show elevation of serum ALT level by aspirin (positive control) and its dose-dependent reversal by plant extract.

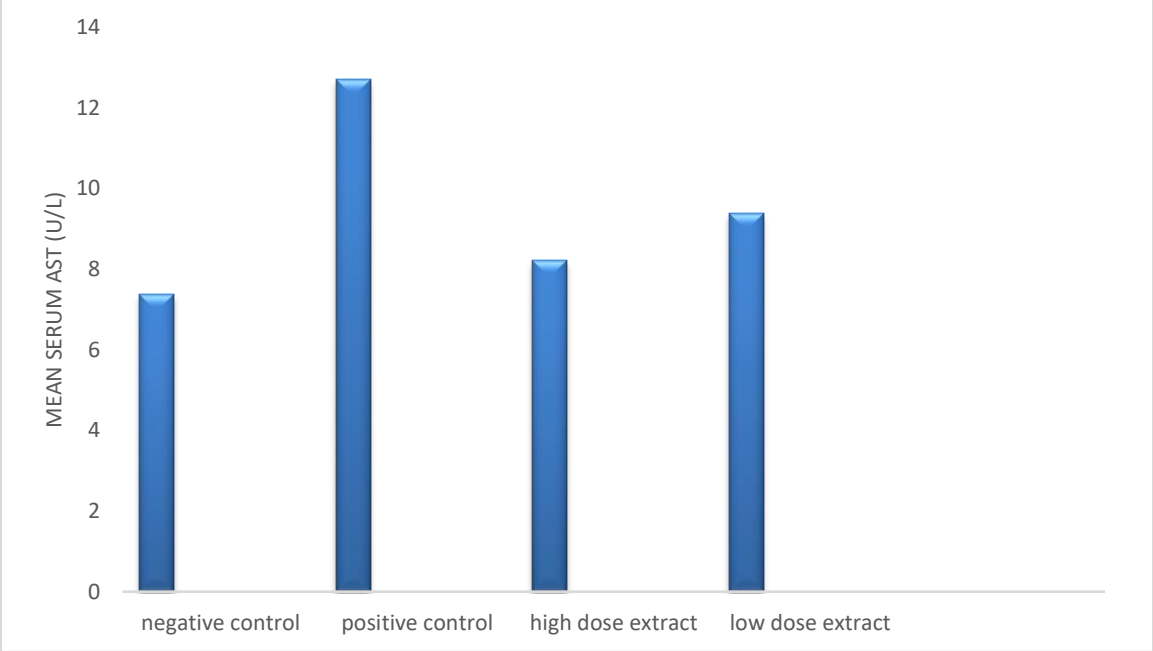

Figure 2: The effect of aqueous extract of Rhizophora racemosa stem bark on serum AST

Results show an elevation of AST level by aspirin (positive control) and a significant dose-dependent reversal by plant extract.

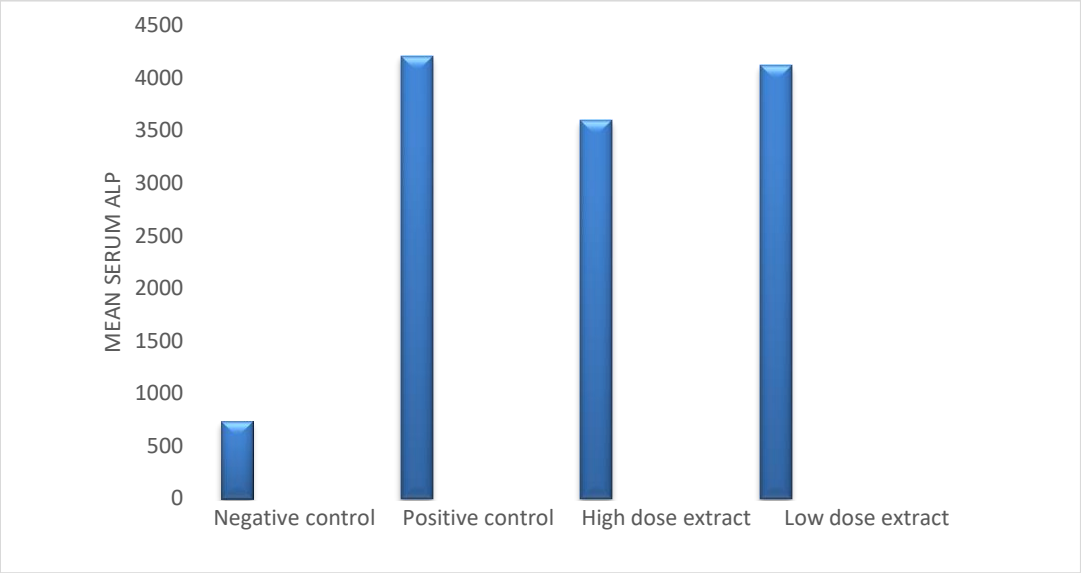

Figure 3: Effect of aqueous extract of Rhizophora racemosa stem bark on serum ALP

Results show an elevation of ALP level by aspirin (positive control) and a slight dose dependent reversal by plant extract.

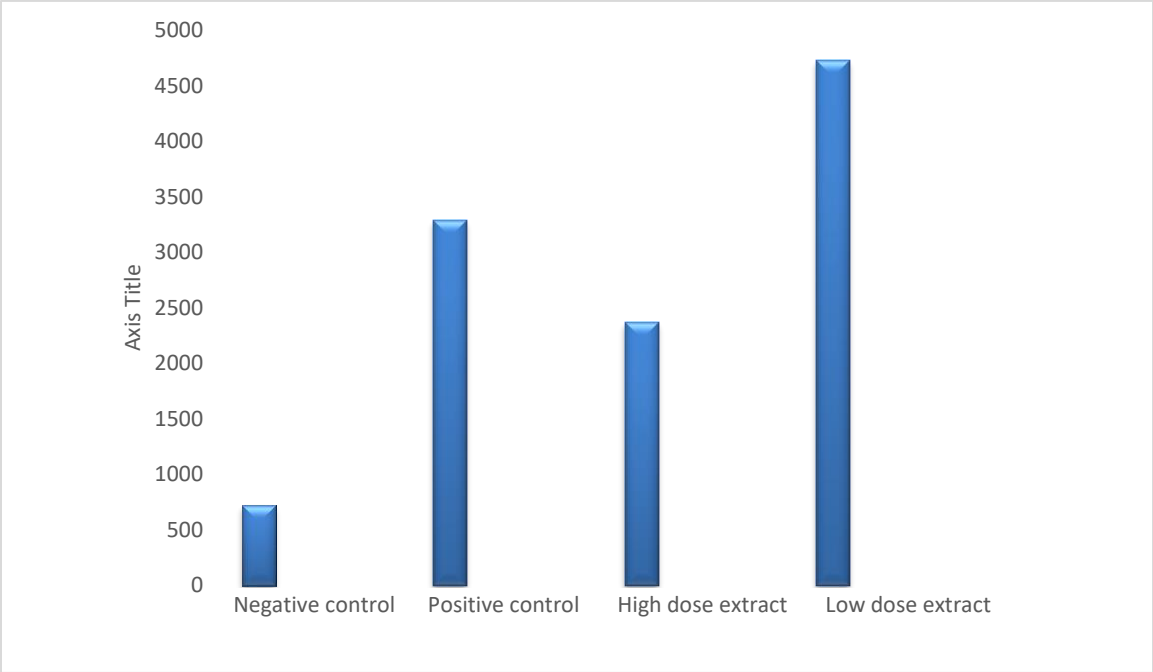

Figure 4: Effect of aqueous extract of Rhizophora racemosa stem bark on serum creatinine

Results show elevation of serum creatinine level by Aspirin (positive control) and its reversal by only high dose of extract.

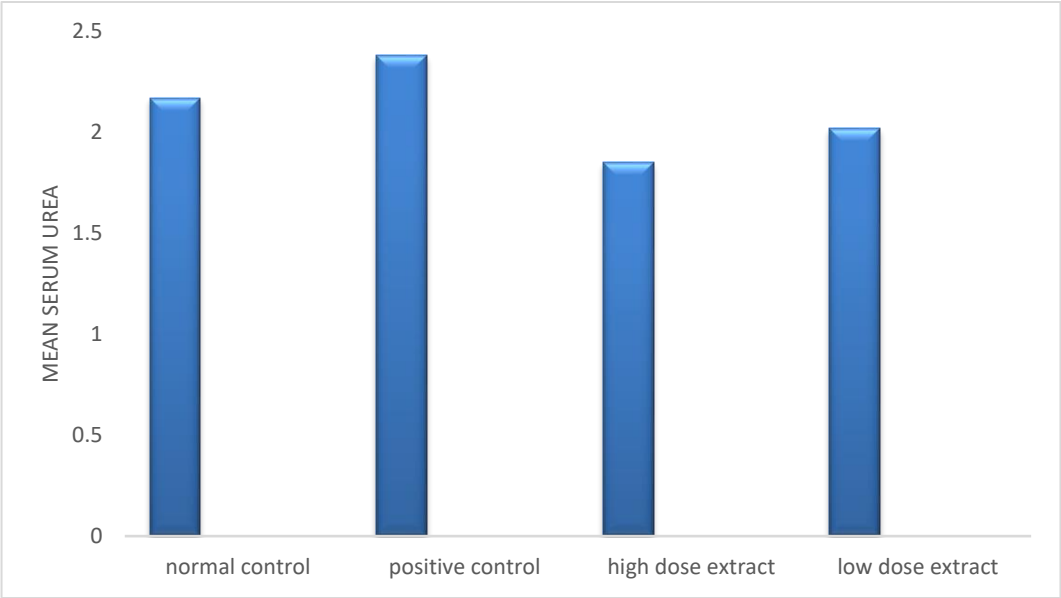

Figure 5: The effect of aqueous extract of Rhizophora racemosa stem bark on serum urea.

Results show elevation of serum Urea level by Aspirin (positive control) and its dose-dependent reversal by high and low doses of extracts.

Discussion

Aspartate aminotransferase is abundant in organs such as the liver, kidney, heart, brain, skeletal muscle and red blood cells while alanine aminotransferase is restricted to the liver. Cell injury by hepatotoxins is through organelle damage, specifically of the smooth endoplasmic reticulum accompanied by failure in bile secretion.

Results obtained from the present study show an increase in AST, ALT, and ALP levels in aspirin-induced hepatic and renal toxicity groups compared to the negative control group (group 1) (figures 1, 2 & 3). Increased levels of serum ALT, AST and ALP point to cellular leakage and loss of membrane integrity of liver cells (Drotman and Lawhan, 1978). This may arise from high dose of aspirin induced hepato-cellular injury. This is in agreement with Yamagata et al., (1966) who reported that high dose of aspirin could lead to peptic ulcer and liver dysfunction and damage.

Results obtained also show a decrease in the level of these enzymes in extract groups. Administration of aqueous extract of *Rhizophora racemosa* stem bark given to groups with aspirin induced liver toxicity suppressed the elevated serum ALT and AST in a dose dependent fashion. However, statistical analysis indicates that while the decrease in AST was significant ($p<0.05$), that of ALT was insignificant ($p>0.05$).

Alkaline phosphatase (ALP) is found principally in the liver, bones, kidneys, and digestive system. The results obtained from the present study (fig. 3) show an increase in serum ALP in aspirin-induced hepatic toxicity groups compared to the negative control group (group I) in a significant fashion ($p<0.05$)). The results also show a decrease in the serum level of ALP in extract pre-treated groups. Aqueous extract of *Rhizophora racemosa* stem bark suppressed the elevated serum ALP in a dose-dependent pattern agreeing with results reported by Shehu and Abubakar, (2018). This shows that if continued, treatment with the plant extract may have a stabilizing effect on the plasma membrane and heal the hepatic tissue damage as suggested by Effiong and Akpan., (2015). This suggests that the extract of *Rhizophora racemose* possesses the ability to reverse hepatic tissue damage. ANOVA analysis carried out on the results shows that while the decrease in ALP in the high-dose extract groups was significant ($p<0.05$), that of low-dose extract was insignificant ($p>0.05$). The results for AST, ALT, and ALP in this study agree with the findings by Umoren et al (2023), who reported elevated levels in aspirin-treated albino rats, which were lowered by *Jatropha tanjorensis* extract. A similar trend of findings was reported for AST and ALT by Akanda, et al (2017) during $NaAsO_2$-induced toxicity treated with *Geranium koreanum.*

Creatinine, the waste product of creatine metabolism is excreted, unchanged by the kidneys through urine. The result shows a significant elevation ($p<0.05$) in serum creatinine level in the untreated group (group II) compared to the uninduced group (group I) (fig. 4). Elevated serum creatinine level is indicative of possible kidney dysfunction. The result also shows a dose-dependent restoration in the level of serum creatinine in the extract groups. This indicates that aqueous extract of *Rhizophora racemosa* stem bark has both liver and kidney protective properties. The decrease in serum creatinine in those of high and low-dose extracts is insignificant ($p>0.05$). These results are similar to findings by Nafiu *et al*., (2011) and Neelima *et al* (2020).

Representing 90% of urinary nitrogen, urea is the major end product of protein breakdown. Its level is directly proportional to protein intake and inversely to excretion rate. The liver is the site for both deamination of amino acids and the urea cycle which converts ammonia to urea.

The result shows an increase in serum urea level in aspirin-induced liver and kidney toxicity group compared to the negative control group (group I) (fig. 5). This could be as a result of damage to the glomerulus of the kidney which diminishes the glomerular filtration leading to urea retention. (Clarkson, 2004). The result also shows a decrease in the level of serum urea in extract pre-treated groups. Administration of *Rhizophora racemosa* stem bark extract to groups with aspirin-induced liver and kidney toxicity suppressed the elevated serum urea in a dose-dependent but insignificantly ($p>0.05$). A similar pattern of response was reported by El-Sheikh et al (2022) for values of creatinine and urea in Aspirin-induced rats treated with thymol, and also by Chinnappan, et al (2019) during paracetamol induced nephrotoxicity in rats treated with *Eurycoma longifolia.*

Conclusion

The study shows that aspirin precipitated considerable hepatic and renal toxicity as evidenced by the sharp rise in the values for all five (5) investigated parameters (ALT, AST, ALP, Urea, and Creatinine). Furthermore, the results clearly indicate that aqueous extract of *Rhizophora racemosa* stem bark possesses inhibitory properties against aspirin-induced hepatorenal toxicity.

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- Conceptualization and methodology: BA & AFO.
- Performed experiment: SAC & EIM.
- Analysis of data: AFO, SAC & EIM.
- Writing-original draft preparation: AFO, SAC & EIM.
- Project administration: BA & SAC.
- Reagents & materials: BA, SAC & EIM.
- Writing-review and editing: AFO.

All authors have read and agreed to the published version of the manuscript.