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Research Article

Histopathologic and functional studies of the liver and kidneys of albino rats treated with ethanol crude extract of *Sida acuta* (wire weed) leaves in Nigeria

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Abstract

More than 80% of developing countries' populations depend on herbal medicine for their health care needs. Studies have revealed that *Sida acuta* is used for the treatment of various ailments. Hepatotoxicity and renal toxicity of ethanol crude extract of *Sida acuta* leaves in albino rats. Ethical approval was properly obtained. Twenty adult male albino rats were divided into 5 groups (A-E) of 4 rats per group. Groups A and B received water and 10% ethanol respectively and served as controls. Groups C–E received graded doses of the extract 50, 100 and 200 mg/kg body weight respectively via oral gavages for 21 days. Serum levels of total bilirubin, Alkaline Phosphatase (ALP), Aspartate Transaminase (AST) and Alanine Transaminase (ALT) were estimated for hepatotoxicity, while Serum urea and electrolytes (sodium, potassium, chloride and bicarbonate ions) were estimated for renal toxicity. The livers and kidneys were excised for subsequent histopathological processing and photomicrography. There was a statistically significant increase in the total bilirubin, AST, ALT and ALP reactivity among treated rats in groups C and D compared to controls, $p = 0.04$ respectively. There were no significant differences in the serum electrolytes and urea of treated groups compared to controls, $p > 0.05$. Histopathological changes were consistent with toxic injuries noticed on the liver and kidney tissues of the treated rats. In conclusion, the results revealed that prolonged oral intake of ethanol leaf crude extract of *Sida acuta* can exert hepatic and kidney damage on rats and can be extrapolated to men. There is a need for monitoring of *Sida acuta* use in humans.

1. Introduction

Sida acuta (broom weed) is a perennial, branched, and erect shrub. It has a woody tap root, hairy branded up to 1 m high. It reproduces by regeneration and from seeds. It is referred to tropical weed in cultivated farm, waste areas, and roadsides. In most regions of Nigeria, it is usually regarded as a harsh weed without any form of economic benefit. In most countries, *Sida acuta* plants (teaweed or ironweed) are empathically assumed as 'weeds' [1].

Information obtained from indigenes of Nigeria revealed that traditional herbalists have been using *Sida acuta* for the cure of various disease conditions and symptoms which include malaria, fever, headache, infectious diseases and rheumatism.

Different revelations from different countries have confirmed the important and positive effects of this weed in healthcare delivery. *Sida acuta* is widespread commonly, within tropical areas and its importance in traditional management and/or treatment of different ailments has been reported by many researchers [2]. The relevance of *Sida acuta* for the treatment and management of disease conditions such as colds, renal inflammation, ulcers, fever, headache, asthma, and worm infections in Central American regions has been revealed [3]. Additionally, study reported that juice from the leaf of *Sida acuta* has antihelmitic effects on digestive system parasites [4]. Alkaloids, steroids, terpenoids and flavonoids were identified in moderate levels in the methanolic extract of *Sida acuta,* while saponins, glycosides and tannins were absent [5]. Phytochemical analysis of ethanolic extract of the *Sida acuta* leaves in a previous study detected the following; Tannin, alkaloid, saponin, flavonoid, steroid, terpenoid, and cardiac glycoside. Vitamins present in the extract were thiamin, niacin, ascorbic acid, tocopherol, and riboflavin. Mineral components are calcium, magnesium, and Zinc [6].

1.1 Specific toxic components of Sida acuta

1.1.1 Terpenoids toxicosis

Terpenoids have eight major subclasses, classified according to carbon numbers and isoprene units. Most of the terpenes, basically the monoterpenes, have high cytotoxic abilities as revealed in experimental models [7]. Studies revealed that digoxin, cicutoxin, daphnetoxin, gibberellic acid, and atractyloside, are the five most toxic terpenoids [8].

1.1.2 Flavonoids/Phynolics toxicosis

Exposures to flavonoid/phenolic oral intake has been the cause of toxic flavonoid–drug interactions, contact dermatitis, anemia due to hemolysis, liver failure, and estrogenic-related cases such as breast cancer, and male reproductive health [9].

1.1.2.1 Flavonoid–drug interactions

Inactivation of CYPs, which are needed for carcinogen activation, is an important chemopreventive effect of various flavonoids, but may be a possible toxic characteristic in flavonoid–drug interactions [9].

1.1.3 Tannin toxicosis

Food intake of high-tannin content diets in rats caused severe growth retardation is well documented [10]. Studies showed that tannins are identified in large quantities in the extracts of *S. acuta* Burn f. and *S. cordifolia* L [11].

1.1.4 Alkaloid toxicosis

1.1.4.1 Tropane alkaloids

Tropane alkaloids are found in all plant parts and with higher concentrations in younger plants. However, the quantity of each alkaloids differ prominently according to plant type, species and varieties [12].

1.1.4.2 Pyrrolizidine alkaloids (PAs)

Pyrrolizidine alkaloids (PAs) can be hepatotoxic, pneumotoxic and genotoxic compounds. Structurally, they contain the pyrrolizidine group [13]. They can cause hepatocyte necrosis and liver failure. Various PAs are potential carcinogens at lower doses that can cause liver cell necrosis. Some can adversely attack the lungs [14-15]. Extracts of green tea are increasingly causing liver failure as it is included in more products [16-17].

1.2 Hepatotoxicity

The liver being a major metabolic organ only present in vertebrates, performs many important biological functions including; detoxification, synthesis of proteins and biochemical needed for digestion and growth [18-19]. Metabolism and proximity to the gastrointestinal tract make the liver susceptible to injury from drugs and other substances. About 75% of blood moving directly from the gastrointestinal organs and the spleen through the portal veins brings drugs and xenobiotics in near-undiluted form.

Most chemicals damage mitochondria, which produces energy. Dysfunction of the mitochondria produces excessive quantity of oxidants that later cause hepatotoxic. Stimulation of various enzymes in the cytochrome P-450 system, such as CYP2E1 also causes oxidative stress [20]. After approval, drugs are commonly withdrawn from the market due to acute and/or chronic drug-induced liver injuries.

Liver injuries ensue when there is increase in either; Alkaline Phosphatase (ALP) level > twice ULRR, Alanin Transaminase (ALT) level > three times of

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upper limit of reference range (ULRR), or total bilirubin level > twice ULRR when associated with increased ALT or ALP [21-22]. Examples of alternative/herbal remedies that can be hepatotoxins are; Ackee fruit, Camphor, Bajiaolian, Copaltra, Garcinia, Cycasin, [23] Kava leaves, Horse chestnut leaves, pyrrolizidine alkaloids, Comfrey, Valerian [24-25] Chinese herbal remedies; Jin Bu Huan, Shou Wu Pian, Ephedra, Bai Xian Pi [26-27].

1.3 Histopathologic changes in the liver toxicity

1.3.1 Zonal necrosis

Liver cell or hepatocyte necrosis can be drug-induced and the commonest type is zonal necrosis. Zonal necrosis is where the injury is largely located in a peculiar region of the liver lobule. It may be elicited by a very high serum level of ALT and serious abnormality of liver function, causing acute liver failure.

1.3.2 Hepatitis

Infiltration of inflammatory cells occurs normally due to hepatocellular necrosis. Drug-induced hepatitis can be divided into three categories; viral hepatitis which is the commonest and shows histological characteristics resembling acute viral hepatitis, focal or non-specific hepatitis showing scattered foci of cell necrosis which may be associated with lymphocytic infiltration, and chronic hepatitis which is closely possess features of autoimmune hepatitis clinically, histopathologically, and serologically.

1.3.3 Cholestasis

Cholestasis is defined as impaired flow of bile from the liver to the duodenum. The two primary types are; obstructive cholestasis, where there is a mechanical blockage in the duct system due to a gallstone or malignancy, and metabolic cholestasis, in which there are problems in bile formation which may be due to genetic defects or acquired as an adverse outcome of various drugs. Cholestasis is normally accompanied by poisonous bile acid accumulation in the hepatocytes or systemic circulation [28-31].

1.3.4 Steatosis

Steatosis, also regarded as "fatty change" is an abnormal accumulation of fats (lipids) within a cell or organ [32]. The liver is a primary organ of lipid metabolism. Hence, steatosis most commonly occurs in the liver, where the condition is usually referred to as fatty liver disease. Steatosis can also affect other organs, like the kidneys, muscles, and heart [33]. The word 'steatosis' is normally related to liver disease when the organ is not specified [34].

1.3.5 Granuloma

This can be drug-induced in the liver and other organs. Patients normally present with features of systemic vasculitis and hypersensitivity. As much as over 50 drugs have been associated with granuloma. They include; phenytoin, allopurinol, isoniazid, quinine, quinidine, and penicillin. A granuloma is an aggregation of macrophages (along with other cells) that forms in response to chronic inflammation. This occurs when the immune system fights to isolate foreign substances but it is otherwise unable to eliminate the foreign body [35].

1.3.6 Vascular lesions

Vascular lesions arise following injury to the vascular endothelium. It can be induced by venoocclusive disease, chemotherapeutic agents (bush tea), Hepatic vein thrombosis (Oral contraceptives), Peliosis hepatis (Anabolic steroids).

1.3.7 Neoplasm

Prolonged exposure to some factors, toxins or medications can cause neoplasms. Hepatocellular carcinoma, liver adenomas, and angiosarcoma are commonly reported. Causes can be anabolic steroids, vinyl chloride, arsenic, combined oral contraceptive pills, and thorotrast.

1.3.8 Hydropic degeneration

Hydropic degeneration often means severe cellular damage due to viruses. It is a more severe or advanced form of cellular swelling. Two types of hydropic degeneration are:

1.3.8.1 Ballooning Degeneration

The cells may swell up like a balloon prior to their destruction.

1.3.8.2 Vacuolar degeneration

There is a discrete bleb (vacuole) of fluid within the cytoplasm. Vacuolar degeneration mainly occurs in

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cells that are very metabolically active and have well developed pumping mechanisms, such as the hepatocyte, renal tubular epithelium, and pancreatic acinar cell.

1.4 Kidney toxicity

The kidney is a major organ which participates in very important functions such as; detoxification, homeostasis, regulation of extracellular fluids, and excretion of toxic metabolites [36]. Medications and chemicals can cause rapid defects in kidney functions which is referred to as nephrotoxicity. Nephrotoxicity occurs through different mechanisms which could be inflammation, renal tubular toxicity, crystal nephropathy, glomerular damage, and thrombotic microangiopathy [37]. Blood urea and serum creatinine are the traditional biomarkers of nephrotoxicity and renal dysfunction which are specific but have low sensitivity in the detection of early renal damage [38]. Albumin, immunoglobulin G, and transferrin are called high-molecular-weight proteins which are more sensitive in the early diagnosis of glomerular filtration dysfunction, structural glomerular damage and glomerular damage respectively [39]. Low-molecular-weight proteinuria is due to proximal renal tubules damage following failure of the reabsorption capacity [40].

1.4.1 Pathological changes in the kidney toxicity

1.4.1.1 Alterations of renal intraglomerular hemodynamic

Angiotensin-converting enzyme inhibitors (ACEIs) like lisinopril, Non-steroidal anti-inflammatory Drugs (NSAIDs) like diclofenac, Angiotensin II Receptor Blockers (ARBs) like losartan can cause serious defects of intraglomerular pressure and reduction of GFR by affecting the efferent arterioles of glomerulus. Cyclosporine and tacrolimus cause dose-dependent afferent arteriole vasoconstrictions thereby affecting afferent arterioles pressure [41-42].

1.4.1.2 Renal tubular toxicity

The active secretion and reabsorption mechanisms as well as the biotransformation capacity of the renal proximal tubules make the cells of the proximal tubule specifically responsive to drug-induced toxicity and subsequent acute renal injury [38].

1.4.1.3 Glomerulonephritis and interstitial nephritis

Glomerulonephritis can be caused by various nephrotoxic agents including; NSAIDs, gold, hydralazine, interferon, lithium, and pamidronate [43]. Chronic interstitial nephritis can be caused by drugs such as; Chinese herbal medicine, cyclosporine, and NSAIDs (>1 g/day) for 2 years. Initial and early appreciation of this condition must not be neglected, because it may lead to end-stage renal disease [44].

1.4.1.4 Drug-induced crystal nephropathy

Sulfonamides, acyclovir ampicillin, ciprofloxacin, triamterene, and methotrexate, are mostly associated with drug-induced crystals [45]. Significant uric acid and calcium deposition can cause acute renal failure due to chemotherapy in lymphoproliferative diseases [46].

1.4.1.5 Drug-induced thrombotic microangiopathy

Immune response due to drug intake can cause thrombotic thrombocytopenic purpura and platelet activations, which lead to endothelial cytotoxicity as seen in different drug treatments like quinine, cyclosporine, and ticlopidine [47].

1.4.1.6 Drug-induced rhabdomyolysis

Drugs can lead to damage to skeletal muscles following direct toxic effects on the muscle cells or pre-exposure of muscle cells to the toxic effects of strenuous exercise. The damage causes lysis of muscle cells and release of creatine kinase and intracellular myoglobin. Myoglobin can lead to kidney damage due to direct toxic effects and tubular obstructions. Statins, heroin, alcohol, cocaine, and ketamine have been associated with rhabdomyolytic effects [48].

Recently, there has been a surge and preference for alternative medicine treatment over conventional treatments. This cannot be unrelated to adulteration and counterfeit production of conventional drugs especially in countries where drug regulation and proper monitoring are very poor. Poor basic orientation of younger generations, suppression of conscience, lack of morals, corruption and quick, less effort money-making could be the reasons for counterfeit drug production and distribution. These

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medicinal plants owe their treatment potential to some biologically active substances, which present in parts of the plants. The biological active substances are chemicals referred to as active phytochemical substances including; terpenoids, flavonoids, bioflavonoids, benzophenones, and xanthenes. Metabolites also referred to as phytochemicals are; tannins, saponins, cyanates, oxalate and anthrax-quinones [49-50].

In developing countries, African countries, and Nigeria inclusive, herbal medicines still play important roles in health care because they are cheap, readily available and effective [51]. Different plants and plants' parts have been used to treat various types of diseases and infections. More than 80% of developing countries' populations depend on herbal medicine for their healthcare needs [52]. Although the mechanism of action and chemical compositions of most medicinal plants are yet to be fully explored and studied the experience gained with their traditional use over the years cannot be disregarded [53].

Drug toxicity can be easily noticed in the liver and kidneys, functionally, biochemically, and histopathological. *Sida acuta* has LD_{50} > 5000 mg/kg body weight and 3.2 g/kg body weight [54-55] respectively, meaning that it is not easily toxic but there is paucity of information on the histomorphologic effects, hence we studied the hepatotoxicity and renal toxicity of ethanol crude extract of *Sida acuta* leaves in albino rats and this can be extrapolated to man.

2. Materials and methods

2.1 Ethical approval

Ethical clearance approval was obtained from the Faculty of Veterinary Medicine, (Number = FVM-UNN-IACUC-2021-0775) University of Nigeria Nsukka and animals were handled in accordance with protocols approved by the Institutional guidelines on Animal Care and Use Committee. The studies conform to guidelines set by National Institutes of Health on experiments involving the use of animals. The research was carried out from March to April 2021.

2.2 Collection of Sida acuta leaves and processing of leaf extract

Fresh leaves of the *Sida acuta* shrubs were harvested from the University of Nigeria, Enugu campus in southeastern Nigeria. Date of harvest was 5th March,2021. The plant was identified and authenticated by a Botanist at the Department of Plant Science and Biotechnology, University of Nigeria, Nsukka [5]. Enugu State is located in the southeastern region of Nigeria. The leaves were washed and allowed to air dry at room temperature. The dried leaves were ground to a fine powder and kept in a labeled air-tight container until extraction.

Extraction was according to the modified method of [56] with minor modification. Two hundred grams of grounded *Sida acuta* leaves were macerated in 250 ml of absolute ethanol for 72 hours, air tightly covered and labeled. The mixture was filtered and filtrate was concentrated by evaporation in a hot air oven at 37^{0}C. The extract was reconstituted with 250 ml of 10% ethanol to enhance the dissolution of the extract and was kept in the refrigerator as long as the study lasted. The extraction value was 75 mg/ml.

2.3 Experimental animals

Twenty adult male albino rats aged 3 months, weighed 150 – 180 g, were procured and acclimatized for two weeks in metal cages at the animal house of the Department of Human Anatomy, University of Nigeria Enugu Campus. The albino rats were fed with standard rat chow and drinking water *ad libitum* and exposed to 12 hours of light and 12 hours of darkness. The albino rats were divided into five groups (A-E) with four albino rats per group and cage according to approximated body weight. The rats in each group were identified with permanent markers.

Group A received normal water and chow and Group B received 10% of ethanol, both served as controls.

Groups C, D and E received 50 mg/kg body weight (BW), 100 mg/kg BW, and 200 mg/kg BW of extracts respectively, daily for three weeks (21 days). The research was guided by the dosage report from people who used the extract for treatments.

2.4 Serum collection and Animal sacrifice for organ harvest

On the 22nd day, after an overnight fast, the animals were anaesthesized with chloroform fume. Blood

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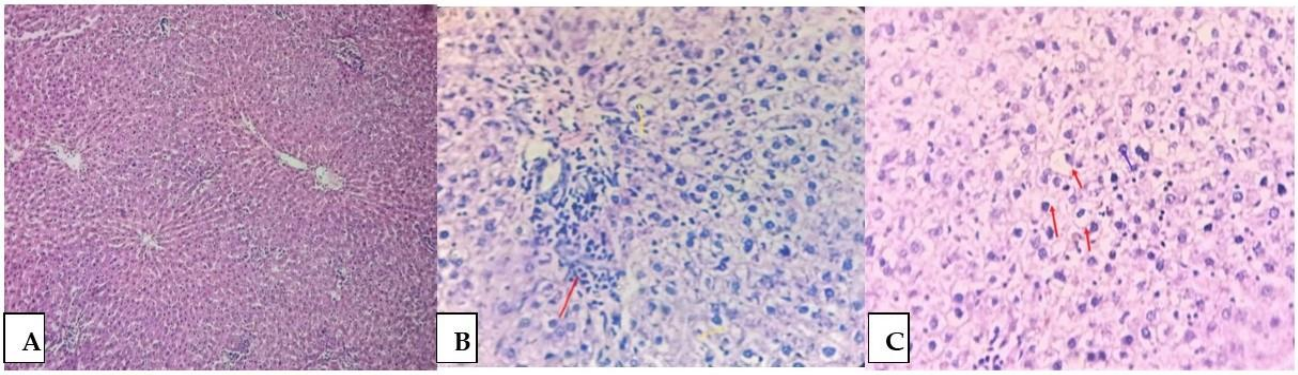

Figure 1. Light photomicrograph of the liver sections. A: [H&E stain x100]: liver section from control rat showing normal liver histoarchtecture; B: [H&E stain x400] liver section from treated rat showing abnormal aggregate of inflammatory cell in the portal tract (red arrow), yellow arrow point at ballooned hepatocytes; C: [H&E stain x400] liver section showing abnormal ballooned liver cells(red arrows).

samples were collected through cardiac puncture into a plain tube for later serum extraction after clotting and retraction of blood samples. The sera were separated into another plain tube and sent for Liver Function Tests (LFT) (Total Bilirubin, Aspartate Transaminase, Alanin Transaminase and Alkaline Phosphatase) and Renal Function Tests (RFT) (Serum Electrolytes, Urea and Creatinine) following standard methods [57]. The liver and kidneys were harvested, and preserved in 10% formal saline for later tissue processing and histomorphologic studies. The livers and kidneys were auto-processed following standard protocol for tissue processing and Heamatoxylin and Eosin staining technique [58]. The results were reported in tables. LFT and RFT were reported in quadruplets, mean±SD. Student's T-test was used for statistical analyses at $p < 0.05$ significant level.

3. Results

Photomicrograph reports in Table 1 show the histology of the liver sections. The controls showed normal histology of the liver whereas the liver tissues from the majority of rats in the treated groups revealed abnormalities in the liver tissues with lesions as reported in the table and seen on the photomicrograph in Fig. 1.

Table 2 shows reports of histomorphology of the kidney sections. Reports from both control groups showed normal histomorphology whereas kidney sections from the treated rats showed varieties of kidney lesions as seen in the photomicrograph in Fig. 2.

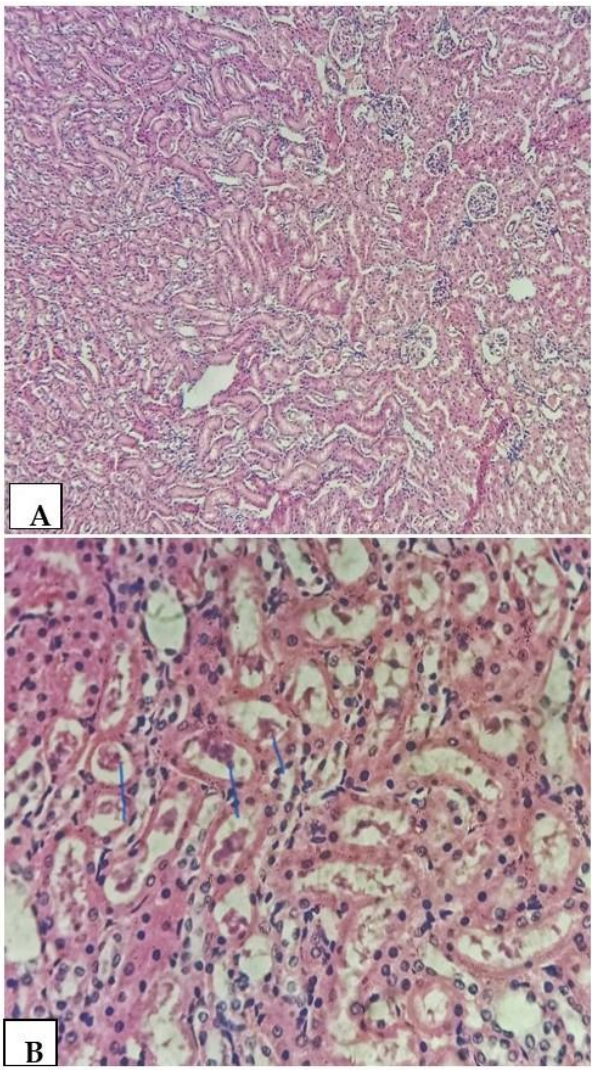

Figure 2. Light photomicrograph of the kidney sections; A: [H&E stain x100] kidney section from control rat showing normal kidney histoarchitecture; B: [H&E stain x400] kidney section from treated rat showing abnormal intraluminal casts (blue arrows).

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Table 1. Histomorphology results of the Liver after 21 days administration of *Sida acuta* leaves ethanol crude extract.

Gorups	Rat 1	Rat 2	Rat 3
GROUP A	Normal architecture of the liver tissues	Normal architecture of the liver tissues	Normal architecture of the liver tissues
GROUP B	Normal architecture of the liver tissues	Normal architecture of the liver tissues	Normal architecture of the liver tissues
GROUP C	Normal central hepatocytes, mild periportal hepatocyte degeneration	Marked periportal hepatocyte degeneration with balloon changes. Loss of normal archtecture	Mild periportal hepatocyte degeneration
GROUP D	Normal architecture of the liver tissues	Mild periportal hepatocyte degeneration with balloon changes	Normal architecture of the liver tissues
GROUP E	Widened sinuses but normal hepatocytes	Widened sinuses. Mild hydropic changes were seen in the hepatocytes	Widened sinuses, Mild periportal degenerative changes

Table 2. Histomorphology results of the Kidney after 21 days administration of *Sida acuta* leaves ethanol crude extract

Gorups	RAT 1	RAT 2	RAT 3
GROUP A	Normal kidney architecture	Normal kidney architecture	Normal kidney architecture
GROUP B	Normal kidney architecture	Normal kidney architecture	Normal kidney architecture
GROUP C	Proximal tubules show mild to moderate tubular injury, luminal cast and loss of epithelial cells Normal distal tubules and stroma	Proximal tubules showed mild tubular injury. Normal distal tubules and stroma	Normal glomeruli Normal tubules and stroma
GROUP D	Glomeruli showed mild increased cellularity	Normal kidney architecture	Tubules shows intraluminal cast and some tubular necrosis
GROUP E	Moderate tubular injury Stromal oedema	Mild tubular injury	Stromal oedema

Table 3 shows the effect of the ethanol crude extract of *Sida acuta* leaves on the liver total bilirubin and liver marker enzymes. There was no significant difference comparing LFT of group A and group B which served as the controls. There was a statistically significant increase in the total bilirubin, AST and Alkaline phosphatase of rats treated with low dose (50 mg/kg BW), (group C) compared to controls, $p = 0.04$. There was also a significant increase in the serum total bilirubin, AST and ALP activities in Group D (normal dose/100 mg/kg BW) compared to controls, $p = 0.04$. There was no significant difference in group E (double dose/200 mg/kg BW) compared to controls, $p > 0.05$.

Table 4 shows that there were no significant differences in the serum electrolytes and urea of treated groups compared to the results of controls, $p > 0.05$.

4. Discussion

This study aimed to investigate the potential hepatotoxicity and renal toxicity of ethanol crude extract of *Sida acuta* leaves in albino rats. Herbs are used in medicines because plants contain natural ingredients that can promote health and alleviate disease conditions. There will always be high risks due to unmonitored formulation of the drugs or when self-medication leads to abuse [59].

The histomorphology results of the present study showed that the oral administration of the ethanol leaf crude extract of *Sida acuta* caused noticeable lesions on the liver tissues and kidney tissues of treated albino rats. The ballooning changes seen on the hepatocytes are signs of liver necrosis. The aggregates of inflammatory cells seen around the portal tracts were a result of inflammatory response. It was reported that

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Table 3. Liver Function Test results after 21 days administration of *Sida acuta* leaves ethanol crude extract

Groups	Total bilirubin (mg/dl)	Aspartate transaminase (U/L)	Alanin transaminase (U/L)	Alkaline phosphatase (U/L)
GROUP A	0.40±0.11	55.8±5.05	33.2±3.46	76.4±4.11
GROUP B	0.45±0.21	60.3±5.02	30.5±1.22	80.1±3.33
GROUP C	0.59±0.06*	65.3±5.22*	29.2±2.15	129.4±4.32*
GROUP D	0.50±0.13*	66.2±4.32*	30.2±2.89	91±2.24*
GROUP E	0.31±0.04	59.0±3.10	32.3±2.78	84.4±4.56

Table 4. Kidney Function Test results after 21 days administration of *Sida acuta* leaves ethanol crude extract

Groups	Serum sodium (mmol/L)	Serum potassium (mmol/L)	Serum chloride (mmol/L)	Serum bicarbonate (mmol/L)	Serum urea (mmol/L)
GROUP A	114.43±13.25	5.8±1.05	90.97±8.15	15.73±0.43	7.00±0.3
GROUP B	115.67±4.90	5.3±1.02	99±8.22	18.81±1.54	8.01±3.33
GROUP C	130.8±0.0	5.3±1.22	102.45±2.77	21.54±6.22	8.75±1.12
GROUP D	126.25±16.05	6.2±1.32	101.45±7.99	20.59±10.83	9.15±2.86
GROUP E	134.0±18.31	5.0±1.10	112.80±10.34	21.25±6.63	10.69±1.21

the leaves of *Sida acuta* contain moderately high concentrations of toxicants and the consumption of these leaves over a period can lead to bioaccumulation of toxicants [60].

The biochemical analyses from the present study showed a significant increase in the serum ALP, AST and serum total bilirubin. Values were slightly above the reference ranges of albino rats (total bilirubin = 0.2 – 0.55 mg/dl; ALP = 56.8 – 128 IU/L). There was also significant increase in serum total bilirubin, serum AST, and ALP comparing the treated albino rats in group C and D to controls and this correspond with the reports of [54, 55] who also reported significant increase in AST, ALT and ALP, though [54] concluded that *Sida acuta* leaf extract was nontoxic because of high LD_{50}. They used whole plants for the aqueous acetone extraction and no histomorphology report.

The result of the present research was in contrast to previous results by [61] who reported that the administration of ethanol crude extract of *Sida acuta* leaves revealed no structural or functional derangement on the liver of albino rats though their work was for 14 days while the present study was after 21 days. The results of the present study were also in contrast to the result of [62] who concluded that the methanol crude extract of *Sida acuta* roots possesses hepatoprotective effect on paracetamol overdosed induced liver damage in Wistar rats. The histomorphology of liver in the present study coincides with the report [55].

Serum AST and ALT are sensitive indicators of liver damage or injury. The ratio of AST to ALT can be useful in indicating the causes of liver damage, while elevated level of only AST is not specific for liver damage since it can also be used as marker of cardiac damage [63]. However, increase in the serum total bilirubin and the liver enzyme activities coincided with the lesions observed in the liver tissues of the treated albino rats in the present study.

Histomorphology of the kidney from treated albino rats showed the range of abnormalities which included; mild to moderate tubular injury, luminal cast and loss of epithelial cells. Tubules showed intraluminal cast and some tubular necrosis. Glomeruli showed mild increased cellularity. Stromal oedema was noticed in the kidney of the treated albino rats. However, there was no significant change in the serum electrolytes and serum urea which can occur, only when ≥ 50% of the nephrons are damaged [64]. The present report is similar to the reports by [55] who used fractions of the *Sida acuta* leaf extract and reported abnormal histomorphology of the kidney but no significant change in the serum electrolyte, urea and creatinine among treated rats. However, [65-66] reported mild changes in serum electrolytes, urea and creatinine in rats treated with ethanol extract of *Sida acuta* leaves.

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5. Conclusions

In view of the above reports, it can be concluded that oral administration of ethanol crude extract of *Sida acuta* leaves caused hepatotoxic and renal toxic effects in albino rats which can be extrapolated to man. Hence we discourage oral and/or uncontrolled intake of ethanol crude extract of *Sida acuta* leaves.

Ethical consent

Ethical clearance approval was obtained from the Faculty of Veterinary Medicine (Number = FVM-UNN-IACUC-2021-0775) and animals were handled in accordance with protocols approved by Institutional guidelines on Animal Care and Use Committee and conform to guidelines set by National Institutes of Health on experiments involving the use of animals.

Authors' contributions

Conceptualization, R.I.O. and C.O.O.; Methodology, C.O.O., N.C.A., M.O.M. and V.M.E.; Software, C.O.O., O.S.O., R.I.O., and A.O.O.; Validation, P.U.A., N.C.A. and C.O.O.; Formal analysis, C.O.O., O.S.O., M.O.M. and P.UA.; Investigation, C.O.O., V.M.E., M.O.M. R.I.O. and A.O.O.; Resources, A.O.O., C.O.O., V.M.E., R.I.O. and O.S.O.; Data curation, C.O.O., A.O.O., V.M.E. and N.C.A.; Writing– original draft and preparation, C.O.O. and R.I.O.; Writing – Review & Editing, P.U.A., N.C.A., O.S.O. and A.O.O., Visualization: C.O.O., O.S.O., N.C.A. and P.U.A.; Supervision, C.O.O. and P.U.A.; Project Administration: C.O.O., R.I.O., M.O.M. and V.M.E.; Funding acquisition: R.I.O., C.O.O., N.C.A., A.O.O., O.S.O., M.O.M., V.M.E. and P.U.A.

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Availability of data and materials

All relevant data are within the paper and its supporting information files. Additional data will be made available on request according to the journal policy.

Conflicts of interest

The authors declare no conflict of interest.

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