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TOXICOLOGICAL EVALUATION OF '*AKUSKURA'*, A HERBAL MIXTURE WIDELY ABUSED BY YOUTHS IN NORTHERN NIGERIA

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Abstract
The use of 'Akuskura' mouth gaggle mixture has recently become popular in northern Nigeria. Despite claims of its medicinal application for piles, fever, headache, malaise etc, it's widely believed to be abused due to its psychoactive property. This study, in view of its wide patronage, aimed to investigate the toxic effects of 'Akuskura' mouth gaggle mixture in albino rats. Following the OECD guidelines, acute (48 hours) and sub-acute (28-days) oral toxicity was investigated. Using 0.1ml, 0.2ml and 0.3ml/mgKg-1BW doses of its most popular brand (Zazzau brand), biochemical and hematological parameters of rats were bioassayed. The histological investigation of harvested body organs (brain, liver, and kidney) of rats was then conducted. The study results revealed a 0.86 ml/kg dose as the LD50 of 'Akuskura' mouth gaggle mixture. Hematological assay revealed lower hemoglobin (HGB) levels in all treatment groups compared with the control ($p<0.05$). The levels of platelets (PLT), lymphocytes (LYMP#), and neutrophils (NEUT#) in all treatment groups were significantly higher than those in the control ($p<0.05$) while levels of mean corpuscular volume (MCV) and mixed white blood cells (MXD %) were significantly higher in only the 0.3 ml/kg treatment group ($p<0.05$). Similarly, blood urea and creatinine levels were significantly higher in rats treated with 0.3ml/kg dose of 'Akuskura' mouth gaggle mixture than in the control ($p<0.05$). These results revealed that 'Akuskura' mouth gaggle mixture is very likely to cause fatal acute poisoning and death. Sub-acute toxicity study results showed that the mixture is capable of causing anemia, compromised immune state, and renal injury. Higher doses of the mixture are relatively more toxic as they are more likely to cause toxic effects.

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INTRODUCTION

Drugs and substance abuse (DSA) refers to the habitual use of psychoactive substances, including alcohol (UNODC, 2021). The burden of drug abuse has become a public health concern, as the global burden of diseases attributable to alcohol and illicit drug use amounts to 5.4% of the total disease burden (Whiteford *et al.*, 2012). In 2020, 275 million people were involved in drug abuse worldwide. This number is expected to increase by 11% in 2030 (Edward and Sunday, 2021; Okoyo *et al*., 2022).

New psychoactive substances (NPS) are substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat. They are a complex and diverse group of substances often known as either designer or synthetic drugs, or by the more popular but misleading colloquial term of 'legal highs' (Vicknasingam et al., 2020). They tend to be either analogs of existing controlled drugs and pharmaceutical products or newly synthesized chemicals, created to mimic the actions and psychoactive effects of licensed medicines and other controlled substances (Vicknasingam et al., 2020). As of December 2020, the total number of NPSs found in 126 countries was 1,047, three times the number of internationally controlled substances. Despite enormous efforts by regulatory bodies in almost all countries of the globe, the emergence of new psychoactive substances (NPS) has made drug control more challenging (Okoyo *et al*., 2022).

Media reports indicate that NPS use is widespread in Nigeria and Africa, but little empirical research has been conducted on this. Local media outlets have reported the use of plant-based and non-classical substances among young Nigerians and the associated poor mental health. BBC News Pidgin reportage of the National Drug Law Enforcement Agency's (NDLEA) media chat shows that aside from dry pawpaw leaf and seed, people also smoke cassava and plantain leaf, spirogyra, dry human and lizard feces, used Gutter-Water (a cocktail of tramadol, cannabis, codeine, and vodka) and Monkey-Tail (a cocktail of locally-produced gin, cannabis seeds, leaves, stems, and roots), Zakami (Datura metel) seeds, Moringa (Zogale) leaf, mandrakes, sewer gas (hydrogen sulfide gas), nail polish, gun powder (Danjuma et al., 2015; Igonikon, 2018; Dumbili *et al.*, 2020). The report also highlighted that some inhale burnt tyres while others drink a mixture of bleach (sodium hypochlorite solution) and carbonated soft drinks and 10-day-old urine for psychoactive effects (Igonikon, 2018).

Recently, herbal products have emerged as popular drugs for recreational use (WHO, 2004). Reports have shown that various our population now use herbs such as morning glory, salvia divinorum, and nutmeg for euphoric and hallucinogenic experiences (Richardson *et al.,* 2007). In Nigeria, there has been a recent surge in the use of herbal concoctions such as 'adimenu' '*Akuskura'*, '*Shake'* as medicines. Contrary to medical claims by users, they are believed to contain psychoactive substances, as they are known to be very addictive (Soonest Nathaniel, 2022). Responses such as jerking, prolonged sleep, reduced physical activity, vomiting, and dizziness have been reported to accompany their use (Soonest Nathaniel, 2022). Studies have shown that a reasonable number of traditional medicines can cause toxicity after some degree of exposure (Ekpenyong, 2014). Despite the wide use of these herbal concoctions, scientific reports on their safety are lacking. The current study aimed to evaluate the safety profile of '*Akuskura'* herbal concoction in whole animal toxicity evaluation models. The results obtained from this study will provide insight into the toxicological profile that will be used for evaluating the potential risk associated with short- and long-term uses of '*Akuskura'* Mouth gaggle mixture.

METHODOLGY

Sample collection and preparation.

Following a survey, the most popular brands of '*Akuskua'* mouth gaggle (Zazzau brand) were purchased from Kawo motor park, Kaduna State. The '*Akuskua'* mouth gaggle mixture was a dark liquid solution in 60ml amber

color plastic bottle ready for oral use (Figure 1). Appropriate volumes of the drug were collected and mixed with normal saline to create a stock solution (concentration). According to the study design, varying volumes of this solution (stock concentration) were administered orally.

Figure 1: Unlabeled '*Akuskua*' mouth gaggle mixture.

Experimental animals

Twenty-nine (29) albino rats (Ahmadu Bello University) were maintained under standard conditions and fed standard animal feed. The rats were further sorted into 2 sub-groups; acute toxicity study group and sub-acute-toxicity group. The acute toxicity group comprises of 5 rats while the sub-acute toxicity group consisted of 24 rats as follows:

i. Group I: Negative control (NC) group receiving normal saline
ii. Group II - received 0.1ml/kg 'Akuskura'
iii. Group III - received 0.2ml/kg 'Akuskura'
iv. Group IV - received 0.3mlg/kg 'Akuskura'

All procedures involving animals in the current study were approved by the Usmanu DanFodiyo University Animal Ethics Committee, UDUAEC (PTAC/TS/ (AE/OT/78-29). Additionally, before commencement of treatment, an acclimatization period of 24 hours was observed.

Blood sample collection

After the treatment phase was completed, animals were allowed to fast overnight before blood samples were collected via tail vein in a plain and EDTA container on the 29th day (Tijjani et al., 2017). The samples collected in plain containers were then centrifuged at 3000 rpm for 10 min, and serum was collected from all samples afterwards for biochemical analysis. The EDTA-containing samples were immediately transported to the laboratory for hematological assay.

Acute toxicity study

The oral median lethal dose (LD_{50}) was determined in rats following the method described by Lorke (1983) with slight modification. The method was divided into two phases. In the first phase 3 groups of three animals each received the plant extract at doses of 0.1, 0.2, and 0.3 ml/kg body weight orally and was observed for signs of toxicity and death for 24 hours. In the second phase, 3 groups of one animal (rats and mice) each received oral extract doses of 0.4, 0.7, and 1 ml/kg oral doses of the extract. The LD_{50} was determined by calculating the geometric mean of the lowest lethal dose and highest non-lethal dose (1/1 and 0/1).

Thus: $\mathbf{LD50} = \sqrt{\boldsymbol{highest\ non\ lethal\ dose} \times \boldsymbol{lowest\ lethal\ dose}}$

Subacute toxicity test

Wistar rats of both sexes were assigned randomly to four groups (n = 6). In accordance with OECD guideline no. 407 (OECD, 2008), group I received distilled water (0.1 ml/kg), whereas groups II-IV received 01ml, 0.2ml

and 0.3ml/kg doses of '*Akuskura',* respectively. For 28 days, the rats were dosed by oral gavage using a curved, ball-tipped stainless steel feeding needle. At the end of the study, on the 29th day, blood samples were collected for biochemical and hematological investigations before the animals were sacrificed, via cervical dislocation after anesthesia (Jamadagni *et al*., 2015), and body organs were harvested. The brain, liver, kidney, and stomach were harvested and immediately fixed in 10% formalin for histopathological examination.

Hematological assay

As described by (de Kort *et al*., 2020), the hematological parameters were determined using a hematology analyzer M18OT (Mythic 18 2010 – Orphee, Switzerland). The parameters assayed included white blood cell (WBC) count, red blood cell (RBC) count, platelets, hematocrit (HCT), hemoglobin (HB) estimation, mean cell volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and others.

Biochemical analysis

As described by (Gidado *et al*., 2017), blood samples were collected into non-EDTA containers and centrifuged at 3000 rpm for 10 min. The serum samples were analyzed for the liver enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) using ELISA kits (Randox Diagnostic Ltd., north Ireland, UK), as described by (Hadrup and Ravn-Haren, 2020). Serum urea and creatinine levels were also evaluated using the same method.

Histological investigation

Histopathological examination of the brain, kidney, liver, and stomach tissue was performed according to the method described by Maharajan *et al*., (2018). Small pieces (3-5 µm thick) of the tissues were fixed in 10% formalin for 72 h and washed in running water. Samples were dehydrated in an autotechnicon and then cleared in benzene to remove the alcohol. Embedding was carried out by passing the cleared samples through three cups containing molten paraffin at 50°C and then in a cubical block of paraffin made by the "L" molds. The slides were then stained with hematoxylin-eosin and observed under a microscope at a magnification power of 400X.

Statistical analysis

The biochemical and hematological results obtained from all rats are expressed as mean ± SEM. The results were first tested for normality of distribution using Kolmogorov-Smirnov test, which indicated that the data were normally distributed. Then, one-way analysis of variance (ANOVA) and Tukey's post hoc test were employed to compare normally distributed results of the experimental groups using SPSS V20.0. Only results with differences at ($p<0.05$) were considered significant. Histological results were analyzed through a combination of visual examination and interpretation of tissue samples by a consultant pathologist, Dr Aliyu Salihu of Department of Morbid Anatomy and Forensic Medicine, Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto State, Nigeria.

RESULTS

Acute toxicity

The oral median lethal dose (LD_{50}) of the '*Akuskura'* mixture was found to be:

$$\mathrm{LD50} = \sqrt{highest\ non\ lethal\ dose \times lowest\ lethal\ dose}$$

$$\mathrm{LD50} = \sqrt{0.7 \times 1} \quad = \sqrt{0.7} : \quad = 0.84ml/kg$$

Hematology

HGB values in all treatment groups were significantly lower than the control ($p<0.05$). Conversely, levels of PLT, LYMP#, and NEUT# in all treatment groups were significantly higher than the control ($p<0.05$) while MXD%, MCV, and MCH levels were significantly higher in only the 0.3 ml/kg treatment group ($p<0.05$).

Table 1: Hematological parameters of rats after 28 days of treatment with 'Akuskura'.

PARAMETER	CONTROL		0.1ml		0.2ml		0.3ml	
WBC(/µL)	20.43	±0.40	22.10	±0.26	23.27	±0.25	24.00	±0.10
RBC(/µL)	8.30	±0.36	6.17	±0.29	6.43	±0.40	7.12	±0.10
HGB(/dL)	18.30	±0.52	11.23	±0.25*	10.13	±0.15*	12.23	±0.40*
HCT (%)	40.93	±0.83	37.80	±0.20	39.37	±0.06	41.36	±0.48
MCV(fL)	36.57	±0.51	52.40	±0.53	50.67	±0.58	58.20	±0.35*
MCH(pg)	13.17	±0.29	16.90	±0.17	15.30	±0.26	17.23	±0.50
MCHC(/dL)	27.73	±0.46	28.20	±0.44	29.20	±0.26	30.30	±0.30
PLT(/µL)	600.73	±1.10	724.33	±4.04*	711.33	±0.58*	741.67	±1.53*
LYM%	70.23	±0.25	71.03	±0.15	70.50	±0.44	78.60	±0.53
MXD%	5.27	±0.31	7.23	±0.32	7.20	±0.36	10.70	±0.44*
NEUT%	9.03	±0.06	10.07	±0.12	9.17	±0.12	10.93	±0.12
LYM#	10.27	±0.31	15.20	±0.20*	16.27	±0.38*	19.07	±0.12*
MXD#	2.13	±0.15	1.90	±0.10	1.70	±0.00	2.43	±0.21
NEUT#	1.07	±0.12	1.97	±0.06*	2.23	±0.06*	2.53	±0.06*
RDW_SD	25.90	±0.17	34.03	±0.06	34.20	±0.35	35.77	±0.21
RDW_CV	14.13	±0.15	15.90	±0.17	16.07	±0.12	17.07	±0.12
PDW	8.23	±0.25	8.10	±0.10	9.20	±0.20	10.23	±0.21
P_LCR	8.13	±0.15	9.37	±0.25	11.20	±0.26	12.50	±0.36

**Values differ significantly from the control at $p<0.05$ (one-way ANOVA).*

Key; WBC-white blood cell; RBC-red blood cell; HGB-hemoglobin; HCT-hematocrit; MCV-mean corpuscular volume; MCH-mean corpuscular hemoglobin; MCHC-mean corpuscular hemoglobin concentration; PLT-platelets; LYM- lymphocyte; MXD-monocyte; RDW_SD-red cell distribution width; RDW_CV-red cell distribution width coefficient of variation; PDW- platelet distribution weight; MPV-mean platelet volume; P_LCR-platelet large volume ratio.

Liver Enzymes

AS shown below (Figure 2), changes in serum levels of AST and ALT were not significant across all treatment groups when compared with the control ($p<0.05$) while serum level of ALP, in all treatment groups, were significantly lower when compared with the control ($p<0.05$).

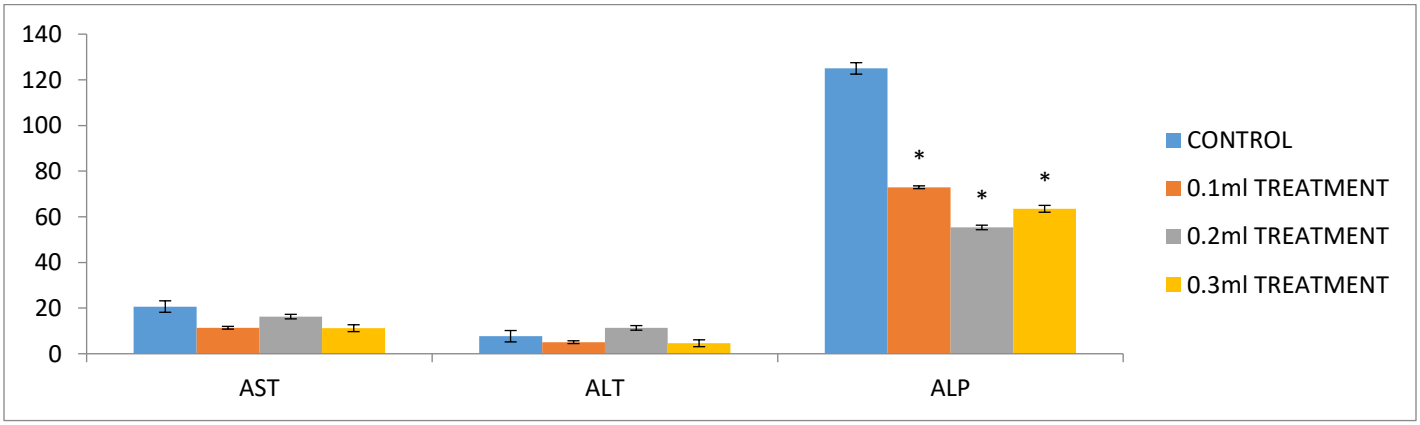

Figure 2: Liver enzyme levels in rats after 28 days treatment with '*Akuskura*' herbal mixture

Serum electrolytes

The table below shows the electrolyte levels in albino rats after treatment with '*Akuskura*' herbal mixture at concentrations of 0.1ml, 0.2ml and 0.3ml/kg. The serum levels of sodium and chloride ions were not significantly higher in rats treated with all doses of '*Akuskura*' herbal mixture compared with the control

($p<0.05$). However, blood urea and creatinine levels were significantly higher in rats treated with 0.3ml/kg dose of 'Akuskura' herbal mixture than in the control ($p<0.05$).

TABLE 2: Serum electrolytes of rats after 28 days treatment with '*Akuskura'* mixture

	EXPERIMENTAL GROUPS			
PARAMETER	**CONTROL**	**0.1ml/kg**	**0.2ml/kg**	**0.3ml/kg**
NA^+ (mmol/L)	122.17±1.89	141.19±0.42	133.50±0.46	148.93±0.12
K^+ (mmol/L)	4.31±0.01	4.90±0.10	4.63±0.06	5.03±0.06
CL^- (mmol/L)	88.87±0.23	90.10±0.46	89.07±0.40	99.04±0.34
Urea (mg/dL)	14.50±0.1	16.20±0.1	18.10±0.1	28.10±0.1*
Creatinine (mg/dL)	0.80±0.1	1.20±0.1	1.10±0.1	5.10±0.1*

* Values are significantly different from control at $p<0.05$ (one-way Anova).

Histology

Brain: The photomicrographs below show similar images of brain tissue from all experimental groups. Similar features of regular brain tissue consisting of neurons, astrocytes, oligodendrocytes, microglia and astrocytes.

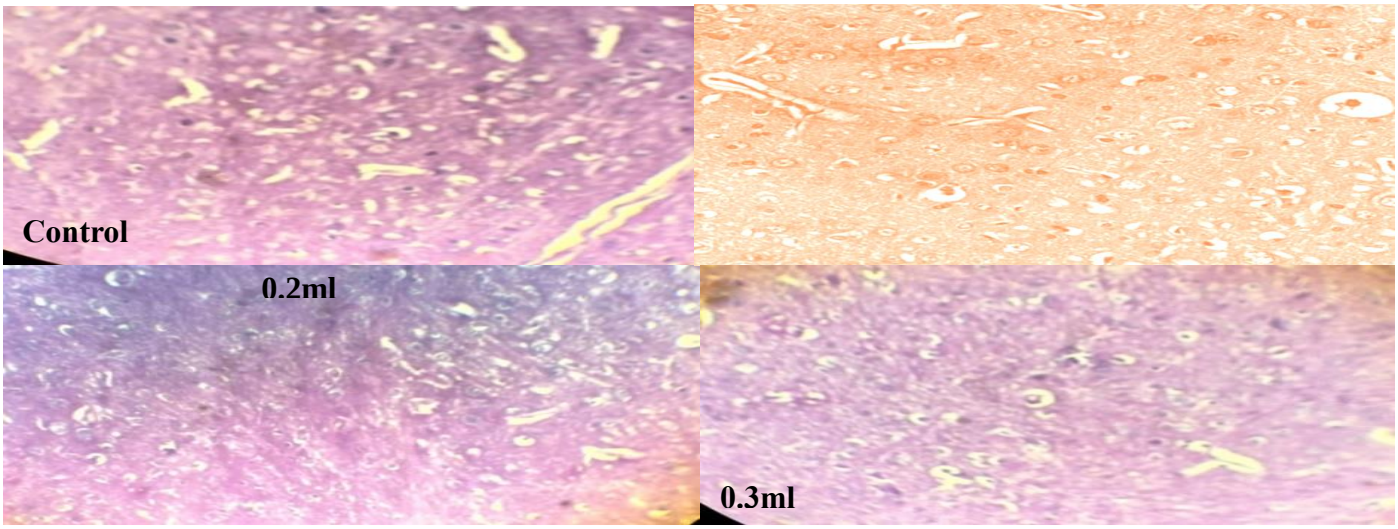

Figure 3: Photomicrographs of rat brain tissue after 28 days treatment with '*Akuskura'* herbal mixture. Magnification ×400

Stomach: The stomach tissue of rats in all experimental groups had a normal architecture (Figure 4). The mucosa was composed of surface epithelium, lamina propria, and muscularis mucosae. No pathological findings were noted.

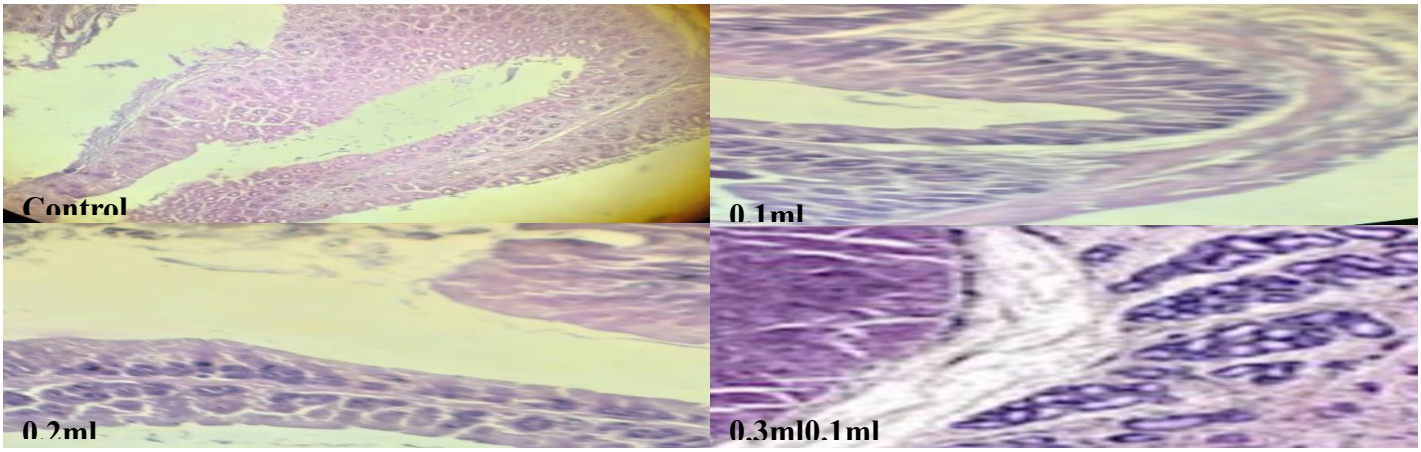

Figure 4: Photomicrographs of rat stomach tissue after 28 days treatment with '*Akuskura'* herbal mixture. Magnification: ×400.

Liver: The figure below shows normal liver tissue with a classical lobule consisting of hepatocytes arranged in plates separated by sinusoids. No pathological findings were observed in any treatment group.

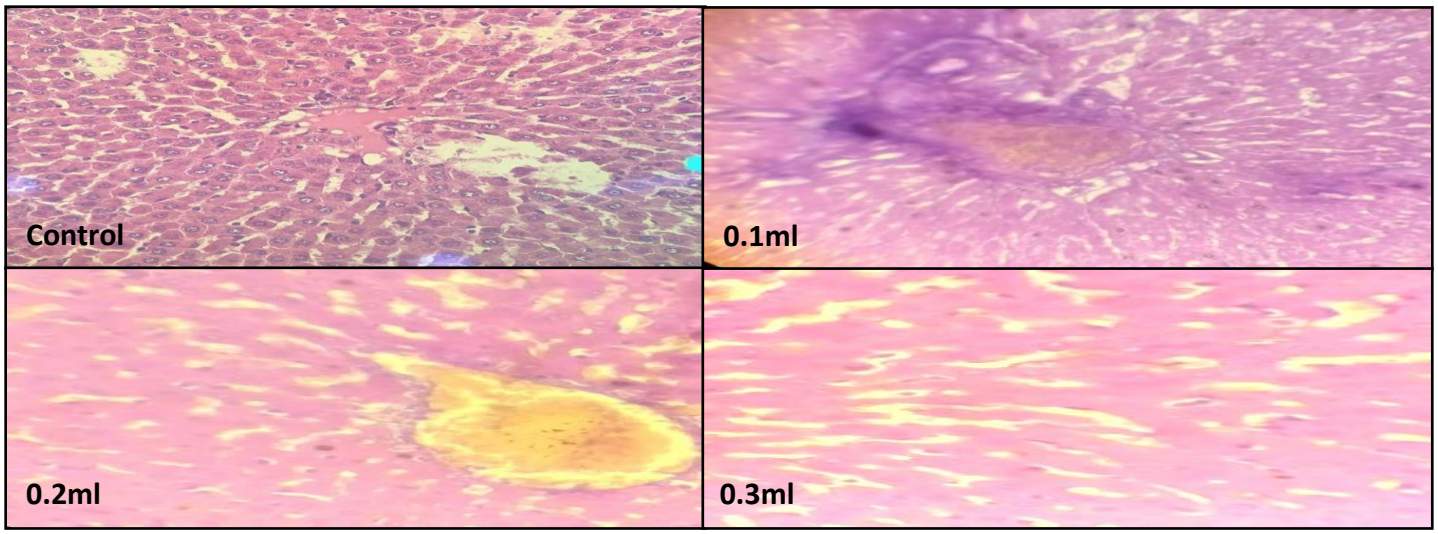

Figure 5: Photomicrographs of rat liver tissue after 28 days treatment with '*Akuskura'* herbal mixture. Magnification: ×400

Kidney tissues: Figure 6 shows kidney tissue with a renal cortex consisting of glomeruli with regular capillary tufts, mesangium, and bowman spaces. No inflammatory activity or pathology was observed in the experimental groups.

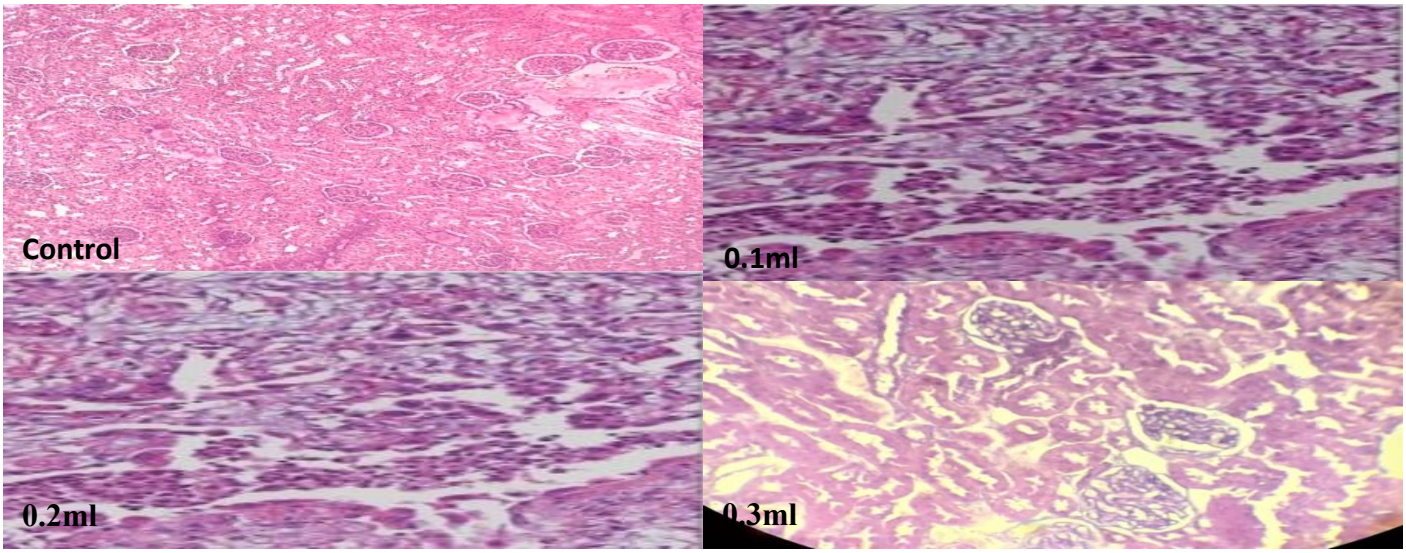

Figure 6: Photomicrographs of rat kidney tissue after 28 days treatment with '*Akuskura'* herbal mixture. Magnification: ×400

DISCUSSION

According to Lorke's postulate, lethal doses of substances are classified according to their LD_{50} values: for $LD_{50} \geq$ 1mg/kg, substance is highly toxic; for $LD_{50} \geq$ 5mg/kg, substance is toxic; for $LD_{50} \geq$ 100 mg/kg, substance is moderately toxic; for $LD_{50} \geq$ 1000 mg/kg, substance is slightly toxic; and for $LD_{50} \geq$ 5000 mg/kg, substance is non-toxic. In this study, oral administration of up to a dose of 0.7ml/Kg^{-1}*BW* of *'Akuskura'* mouth

gaggle mixture did not cause mortality after 24 h of treatment, but other signs of toxicity such as tremors, fits, and loss of balance were visible. However, at a higher dose of 1 ml/kg death was observed. By simple computation, this result gave rise to an LD_{50} of 0.84ml/kg, indicating that, by extrapolation, the extract can be said to be orally toxic. This result could be a logical explanation for the abnormal responses following oral intake of this drug.

Hematopoiesis is the process of blood cell formation involving pluripotential stem cells, which are immature cells with the capability of becoming an erythrocyte (RBC), a leukocyte (WBC), or a thrombocyte (platelet) (Ismail *et al*., 2019). The WBC protects the body from infection by foreign organisms, the RBC boosts the immune system, and the platelets protect blood vessels from endothelial damage and initiate repair of these vessels (Halim *et al*., 2016). Analyzing blood parameters in animal toxicity studies is crucial for evaluating the risk of alterations in the hematopoietic system for its application to humans (Halim *et al*., 2016). Studies have shown that a significant decrease in hematological parameters indicates bone marrow suppression, hemolytic anemia, or thrombocytopenia (Corte *et al*., 2020). In this study, HGB values were significantly reduced while PLT was significantly increased in in all treatment groups of '*Akuskura'* mouth gaggle mixture ($p<0.05$). Conversely, levels of LYMP# and NEUT# in all treatment groups, were significantly increased than the control ($p<0.05$) while values of MXD% was significantly higher in only 0.3ml/kg treatment group ($p<0.05$). By inference, decreased HGB levels indicate reduced RBC counts and, consequently, anemia. This may translate into a compromised immune state, an assertion that can be corroborated by corresponding immune responses resulting in increased levels of LYMP, NEUT, and MXD observed.

The assessment of biochemical parameters can serve as a valuable tool for assessing various body physiological processes and abnormalities (Kim *et al*., 2019). Studies have reported that an increase in these parameters indicates oxidative stress, inflammation, or tissue damage (Manolagas, 2010; Astutie, 2018). In this study, while levels of AST and ALT were preserved, levels of ALP were significantly reduced across experimental groups ($p<0.05$) after administration of '*Akuskura*' for 28 days. Alkaline phosphatases are metalloenzymes of cell membranes that are synthesized in the intestine, liver, bone, placenta, and kidneys. Lower serum ALP levels are often rare and are usually not a source of health concern, whereas higher ALP levels are often indicative of liver or bone disease (Ray *et al.,* 2017). Thus, the study outcome on liver enzymes observed in this study indicated no hepatocellular damage caused by '*Akuskura'* herbal mixture after administration for 28 days.

Botanicals can cause nephrotoxicity via numerous mechanisms, including disrupting renal blood flow, damaging compartments along the nephron, and obstructing urinary flow. A previous study reported increased serum creatinine and urea levels due to decreased clearance and glomerular filtration rate, a phenomenon common to muscle kidney disease (Ekpenyong *et al*., 2014). The impact of '*Akuskura'* mixture on the kidney was also assessed. The serum levels of urea and creatinine in rats treated with the highest dose (0.3ml/kg) were elevated compared with the control ($p<0.05$). Thus '*Akuskura'* herbal concoction is associated with a high risk of liver damage. Histopathological examinations of the brain at all doses (0.1, 0.2 and 0.3 $mlkg^{-1}$) of '*Akuskura'* showed regular neurons surrounded by oligodentrocytes, microglia, and astrocytes across experimental groups, as no pathology was seen. Similarly, photomicrographs of the liver and kidney tissue show normal organ architecture with no pathology.

CONCLUSION

Acute toxicity reports suggest that '*Akuskura'* is likely to cause fatal acute poisoning and death at high doses. However, sub-acute toxicity reports showed that it is capable of causing anemia due to its hematological effects (decreased hemoglobin level). This outcome, given the corresponding increase in leukocytes observed, could

translate into a state of suppressed immunity and consequently increased risk of infection. Furthermore, at high doses, increased creatinine levels indicate possible injury to the kidney.

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COMPETING INTEREST

There are no conflicts of interest to declare**.**

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