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Toxicological Evaluation of '*Shake'*, A Herbal Snuff Widely Abused Amongst Youths in Northern Nigeria

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Absracts: Traditional use of 'Shake', a herbal snuff concoction, has recently become very popular in northern Nigeria. Despite their widespread patronage, in disguise as medicines, reports on their safety are scanty. This study aims to investigate the short term or acute (48 hours) and long-term sub-acute (28-day) toxic effects of 'Shake' herbal concoctions, in albino rats following OECD guidelines. Utilizing 100, 200 and 400 mgKg^{-1}BW doses of the most popular brand (Hajiya Salma), biochemical and haematological parameters of rats were bioassayed. After euthanasia, histological investigations of harvested body organs (brain, liver, and kidney) of rats were conducted. At the end of the study, up to 5000 mgKg^{-1}BW dose, no death of animal was recorded in the acute toxicity test. Haematological assay revealed significantly lower RBC, HGB and HCT levels in all treatment groups compared to control ($p<0.05$), while PLT was significantly lower in only rats treated with 400mg/kg ($p<0.05$). Conversely, levels of NEUT in all treatment groups, were significantly higher than the control ($p<0.05$) while MXD% was significantly higher in only 400mg/kg treatment group ($p<0.05$). At all treatment doses creatinine levels of rats were found to be significantly higher than the control ($p<0.05$) and no changes were seen in the histo-pathological analysis of the brain, liver and kidney. These results revealed that oral administration of '*Shake'* herbal concoction is unlikely to cause fatal acute poisoning. However, sub-acute toxicity reports, which showed decreased RBC, HGB, and HCT levels with a corresponding increase in white blood cells, could directly translate into anaemia and, consequently, compromised immune state. Furthermore, increased creatinine level seen indicates a possible damage to the kidney. Thus, the use 'Shake' herbal concoction carries the potential to causes serious damage to the body.

Keywords: *'Shake', Herbal Snuff, Toxicity, Drug Abuse.*

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I. INTRODUCTION

Drugs and substances abuse (DSA) can be termed as the habitual use of illegal 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 burden of diseases (Whiteford *et al.,* 2012). In 2020, there were 275 million people involved in drug abuse worldwide. This number is expected to increase by 11 percent in 2030 (Edward and Sunday, 2021; Okoyo *et al*., 2022).

Despite enormous efforts by regulatory bodies in almost all the countries of the globe, the emergence of new psychoactive substances (NPS) have made the situation of drug control more challenging (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 analogues 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

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countries reached 1,047, three times the number of internationally controlled substances.

Media reports indicate that the use of NPS has become widespread in Nigeria and Africa. 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 faeces, 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 sulphide 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, there is a surge in the use of a herbal snuff concoction '*Shake'* in northern Nigeria. Contrary its claims of medicinal application for piles, dandruffs, malaria, headaches, and sexual dysfunction, 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, dizziness etc, have been reported to accompany their use (Soonest Nathaniel, 2022). Despite the wide use of these herbal concoctions, scientific reports on the safety are unavailable. This study, in view of the fact that a reasonable number of traditional medicines could cause toxicity after some degree of exposure (Ekpenyong, 2014), aims to evaluate the safety profile of '*Shake'* herbal concoction in whole animal toxicity evaluation models. The results obtained from this study will provide data on the safety/ toxicological profile that could be used for evaluating the potential risk associated with short and long term uses of '*Shake'*.

II. MATERIALS AND METHODS

➢ *Sample Collection and Preparation*

Following a survey, the most popular concoction brands of 'Shake' (Hajiya Salma™) was purchased from the old market Sokoto. The 'Shake' powder was weighed using a weighing balance and mixed with normal saline to create a solution (stock concentration). According to the study design, varying volumes of this solution (stock concentration) were administered to the rats orally. The rats were dosed by oral gavage using a curved, ball tipped, stainless steel feeding needle.

➢ *Experimental Animals*

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

- Group 1 - (Negative control, NC) - received only normal saline
- Group 2 - received 100 mg/kg '*Shake'*
- Group 3 - received 200mg/kg '*Shake'*
- Group 4 - received 400mg/kg '*Shake'*

Before commencement of treatment, acclimatization period of 24 hours was observed.

➢ *Blood Sample Collection*

After the treatment phase was completed, as previously described (Tijjani *et al.*, 2018), animals were allowed to fast overnight before blood samples were collected, via tail vein, in a plain container, and an EDTA container. The samples collected in the plain container were then centrifuged at 3000 rpm for 10 minutes. The serum was collected from all samples afterwards for biochemical analysis. The EDTA containing samples were immediately taken to the haematology laboratory for heamatological assay.

➢ *Acute Toxicity Study*

The oral acute toxicity study of '*Shake'* was carried out using the limit dose method in rats in accordance with organization for economic and community development (OECD) guideline no. 425 (Organization for Economic Development, 2022). Five female rats were used for the study. An animal was picked at a time, weighed and dosed with the equivalent volume dissolved in distilled water via oral gavage. Each animal was observed after dosing for the first five minutes for signs of regurgitation. Each was then observed every 15 minutes in the first 4 hours after dosing, every 30 minutes for 6 hours for behavioral signs of toxicity (changes in skin, hair, eyes, mucous membrane, respiratory, circulatory, autonomic and central nervous system, motor activity, convulsion, tremor, salivation, diarrhea, lethargy or sleep) and within 48 hours for mortality according to the specifications of the OECD (2022).

➢ *Sub-Acute Toxicity Test*

Wistar rats of both sexes were assigned randomly into four groups (n = 6). In accordance with OECD guideline no. 407 (OECD, 2008), group I received distilled water only while groups II-IV received 100, 200 and 400 mg/kg of '*Shake*', respectively. The rats were dosed by oral gavage for 28 days. The weight of all rats was measured weekly. At the end of the study, on the 29th day, blood sample was collected via the tail vein for haematological and biochemical investigations before the animals were sacrificed, via cervical dislocation after anaesthesia (Jamadagni *et al*., 2015), and body organs harvested. The brain, liver, and kidney were harvested and immediately fixed in 10% formalin for histopathological examination.

➢ *Hematological Assay*

As described by (de Kort *et al*., 2020), the haematological parameters were determined using a haematology analyzer M18OT (Mythic 18 2010 - Orphee, Switzerland). The parameters assayed included white blood

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cell (WBC) count, red blood cell (RBC) count, platelets, Haematocrit (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 collected into non-EDTA container were centrifuged at 3000 rpm for 10 min. The separated serum was analysed for liver enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) using ELISA kits (Randox Diagnostic Ltd., north Ireland, UK), a method described by (Hadrup and Ravn-Haren, 2020). Serum urea and creatinine were also evaluated using same method.

➢ *Histological Investigation*

Histopathological investigation of the brain, kidney, liver, were carried out according to previously described method (Maharajan *et al*., 2018). Pieces of the organs (3-5 µm thick) were fixed in 10% formalin for 72 hours and washed in running water. Samples were dehydrated in an autotechnicon and then cleared in benzene to remove absolute alcohol. Embedding was done 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" moulds. It was followed by microtome and the slides were stained with Haematoxylin-eosin and observed under a microscope at a magnification power of 400X.

➢ *Statistical Analysis*

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

III. RESULTS

➢ *Acute Toxicity*

No mortality was observed after administering up to 5,000mg/kg of concoction to rats. Thus LD_{50} >5,000 mg/kg body weight.

➢ *Haematology*

The table below shows the result of the mean values of haematological parameters of rats. RBC, HGB and HCT values, in all treatment groups, were significantly lower than the control ($p<0.05$) while PLT was significantly lower in only 400mg/kg treatment group ($p<0.05$). Conversely, levels of NEUT in all treatment groups, were significantly higher than the control ($p<0.05$) while values of MXD% was significantly higher in only 400mg/kg treatment group ($p<0.05$).

Table 1 Haemotalogical Parameters of rats after 28 Days Treatment with '*Shake'* Herbal Mixture

PARAMETER	EXPERIMENTAL GROUPS			
	CONTROL	**100mg/kg**	**200mg/kg**	**400mg/kg**
WBC(/µL)	15.30±0.1	16.10±0.1	18.10±0.1	16.50±1.2
RBC(/µL)	8.46±0.1	5.95±0.0*	6.20±0.1*	5.30±0.1*
HGB(/dL)	16.17±0.1	12.60±0.1*	13.10±0.1*	12.30±0.1*
HCT(%)	46.10±0.1	34.20±0.2*	35.20±0.1*	32.23±0.1*
MCV(fL)	-54.50±0.1	-57.13±0.1	-57.60±0.1	-58.80±0.1
MCH(pg)	-19.16±0.0	-21.16±0.1	-21.30±0.1	-22.70±0.1
MCHC(/dL)	35.43±0.1	36.57±0.1	36.80±0.1	38.50±0.1
PLT(/µL)	741.33±0.9	1025.33±0.9	1232.67±1.5	227.33±1.2*
LYM%	88.13±0.1	91.00±0.1	92.47±0.1	85.40±0.1
MXD%	3.53±0.1	3.23±0.1	3.40±0.1	9.36±0.1*
NEUT%	-8.40±0.1	-2.23±4,3*	-3.80±0.1*	-5.10±0.1*
LYM#	13.60±0.1	15.33±1.0	10.20±0.1	15.50±0.1
MXD#	0.50±0.1	0.67±0.1	0.40±0.1	0.60±0.1
NEUT#	1.20±0.1	1.40±0.1	1.0±0.1	0.80±0.1
RDW_SD	-28.30±1.0	-37.60±0.1*	-34.47±0.1*	-36.53±0.1*
RDW_CV	14.20±0.1	19.20±0.1*	17.10±0.1*	17.13±0.1*
PDW	-8.50±0.1	-7.80±0.1	-7.40±0.1	-7.63±0.1
MPV	-7.10±0.1	-6.67±0.1	-6.40±0.1	-7.63±0.1
P_LCR	-6.76±0.1	-6.10±0.1	-4.2±0.1	-12.56±0.0*

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

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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-platelet; 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*

The bar chart below (Figure 1) shows the level of liver enzymes. Differences in the serum levels of ALT, AST and ALP were not statistically significant across experimental groups ($p<0.05$).

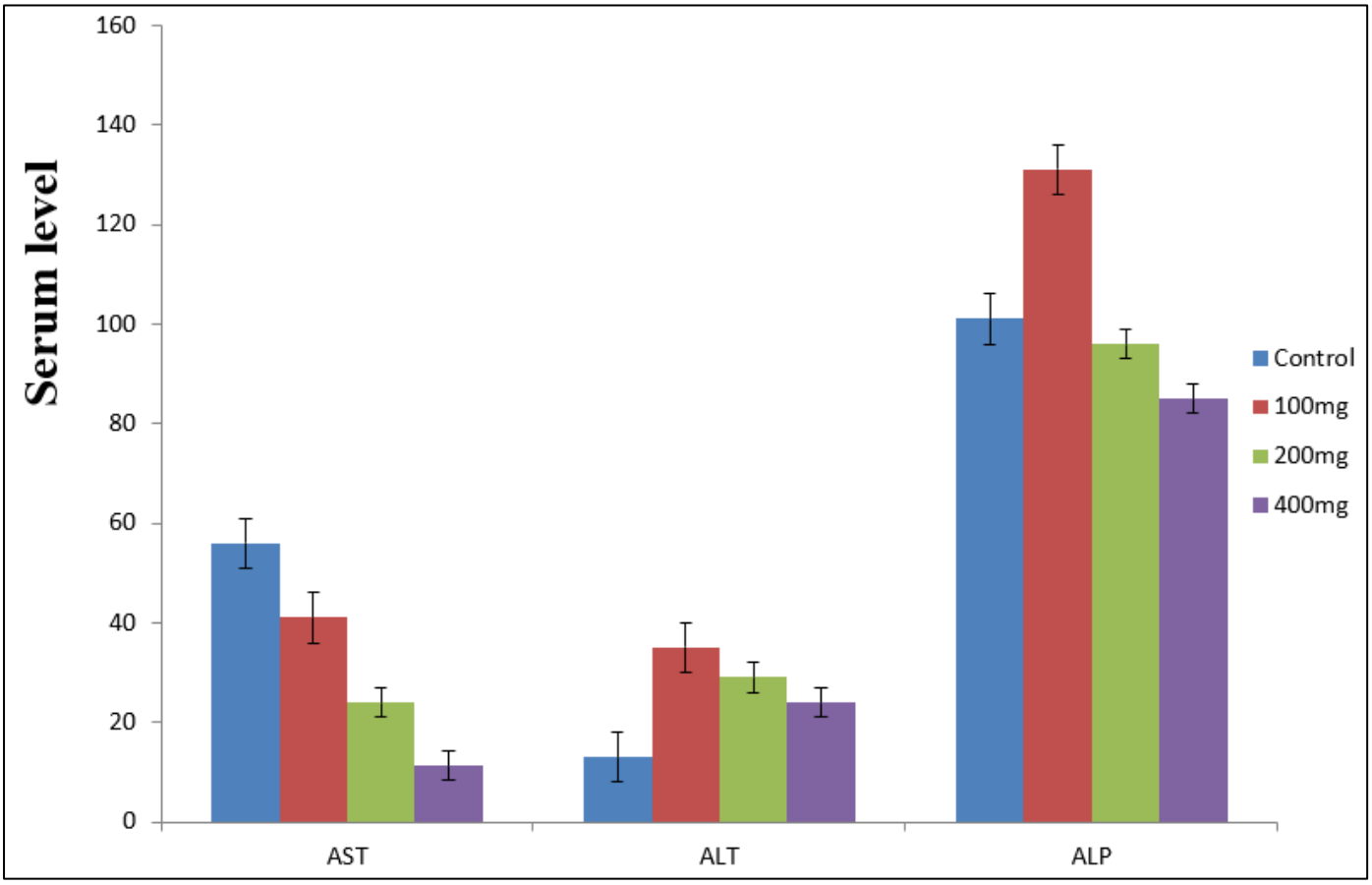

Fig 1 Liver enzymes of rats after 28 days treatment with '*Shake'* herbal mixture

- Key: AST: aspartate aminotransferase;
- ALT: Alanine aminotransferase;
- ALP: Alkaline phosphatase

➢ *Serum Electrolytes*

The table below shows the level of serum electrolytes, urea and creatinine of albino rats after 28 days treatment with '*Shake'* herbal mixture. At all treatment doses (100mg/kg, 200mg/kg and 400mg/kg), serum creatinine levels of rats were found to be significantly higher than the control ($p<0.05$).

Table 2 Serum Creatinine, Electrolytes and Urea of rats after 28 Days Treatment with '*Shake'* Herbal Mixture.

PARAMETER	CONTROL	EXT100mg/kg	EXT200mg/kg	EXT400mg/kg
NA^+ (mmol/L)	137.00±6	142.00±5	142.00±6	136.00±4
K^+ (mmol/L)	6.70±0.1	6.20±0.1	5.50±0.1	9.10±0.1
CL^- (mmol/L)	98.33±3	106.00±5	103.00±6	98.00±3
UREA (mg/dL)	9.50±0.1	9.20±0.1	8.10±0.1	8.10±0.1
CREATININE (mg/dL)	1.40±0.1	5.20±0.1*	8.10±0.1*	8.10±0.1*

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

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➢ *Histopathology*

- **Brain**: Micrographs of brain tissue showed regular neurons surrounded by oligodentrocytes, microglia and astrocytes across groups. No pathology was seen across experimental groups.

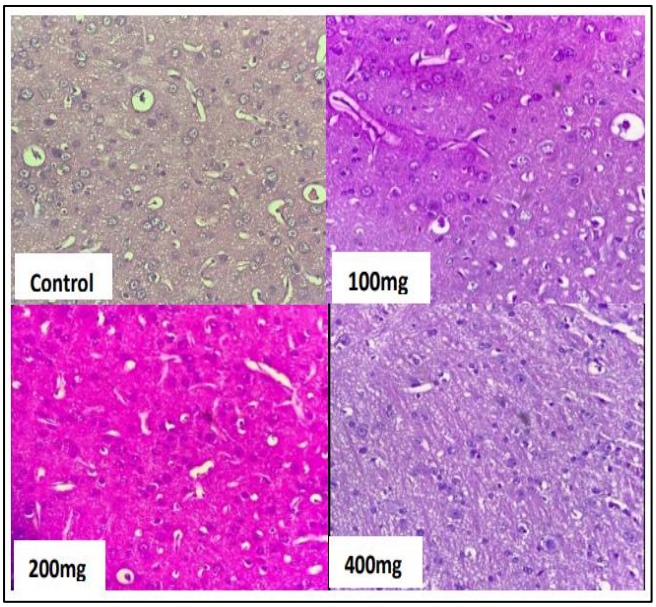

Fig 2 Photomicrographs of Brain Tissue of rat after 28 Days Treatment (Magnification:x400)

- **Liver**: Micrographs of liver tissue showed classical lobule consisting of hepatocytes arranged in plates separated by sinusoids. No pathology was seen across experimental groups.

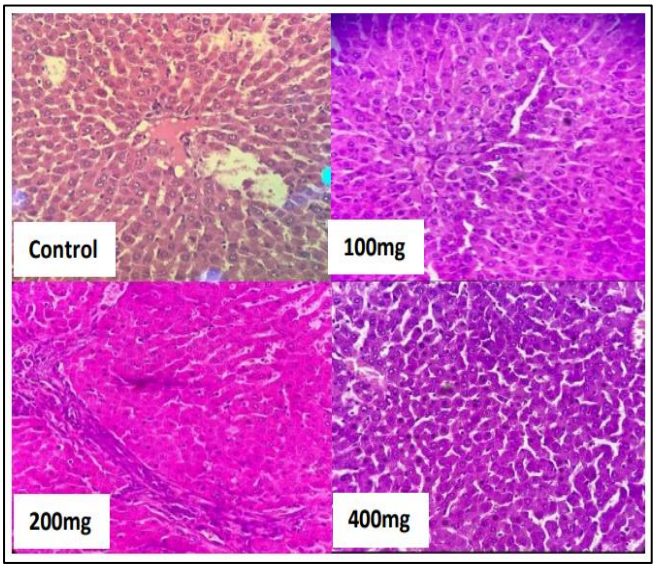

Fig 3 Photomicrographs of Liver Tissue after 28 Days Treatment (Magnification:x400)

- **Kidney**: Micrographs of renal tissue showed cortex and medulla containing regular glomeruli and tubules, respectively. No pathology was seen across experimental groups.

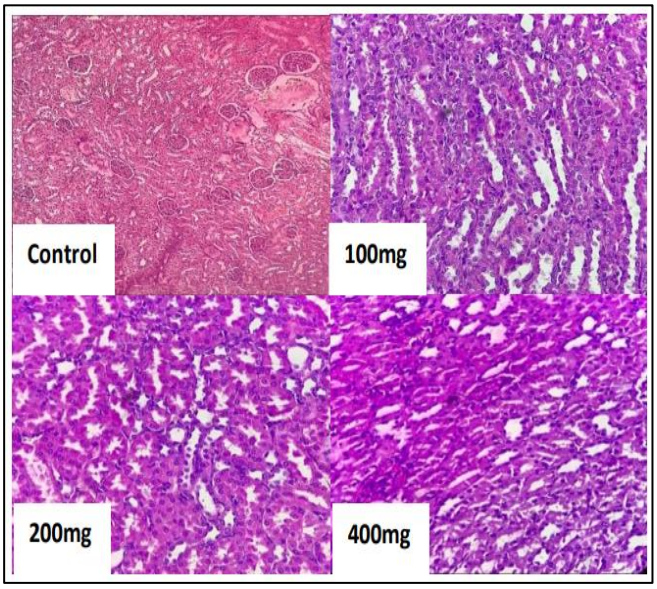

Fig 4 Photomicrographs of Kidney Tissue of rat after 28 Days Treatment (Magnification: x400)

IV. DISCUSSION

Oral administration of up to 5000 mg/Kg^{-1}*BW* dose of *'Shake'* did not cause mortality or any obvious sign(s) of toxicity in rats during the 48 hours of acute toxicity study. According to OECD criteria under Globally Harmonized Classification System (GHS) for chemical substance and mixture, substance with LD_{50} > 2000 and or 5000 mg/kg are categorized as unclassified (Organization for Economic Development, 2001). This suggests that the oral LD_{50} of agents being greater than 2000 mg/kg may be safe. Thus, '*Shake'* herbal concoction can be considered to be non-toxic following acute oral administration.

Analyzing blood parameters in animal toxicity studies remains crucial in evaluating the risk of alterations of the hematopoietic system for necessary application to humans (Halim *et al*., 2016). Studies has shown that significant increase in haematological parameter indicates bone marrow suppression, hemolytic anemia or thrombocytopenia (Corte *et al*., 2020). In addition, anemia is the most prevalent chemotherapy associated haematological toxicity followed by neutropenia in breast cancer patient receiving paclitaxel (Zhao *et al*., 2022). In this study, RBC, HGB and HCT values, in all treatment groups, were significantly reduced when compared with the control ($p<0.05$) while PLT was significantly reduced in only rats that received 400mg/kg of 'Shake' herbal concoction ($p<0.05$). Conversely, levels of NEUT in all treatment groups, were significantly higher than the control ($p<0.05$) while values of MXD% was significantly higher in only 400mg/kg treatment group ($p<0.05$). Thus, by inference, decreased levels of RBC, HGB and HCT indicate haematotoxic by '*Shake'* herbal concoction which may translate into compromised immune state, an assertion that can be corroborated by a corresponding increase in the levels of NEUT and MXD as possible immune responses.

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Biochemical parameters serve as indicators of various physiological processes and body function. They are used to assess normal body function and detect abnormalities in normal body physiology (Kim *et al*., 2019). Studies have shown that an increase in these parameters, which could be either be as a result of exposure to drugs (xenobiotics) or toxins, indicates oxidative stress, inflammations or tissue damage (Astutie, 2018). In 2012, Tarkang *et al*., (2012) reported that ethanol extracts of *Carica papaya* caused a significant dose-dependent increase in AST in experimental animals after administration of the ethanol extract for 28 days which indicated cellular damage to the liver. In this study, changes in liver enzymes (AST, ALT, and ALP) across experimental groups were not significant ($p<0.05$) after administration of '*Shake*' for 28 days. Thus, 28 days oral administration of '*Shake'* herbal concoction caused no hepatocellular damage.

Botanicals can cause nephrotoxicity via numerous mechanisms, including disrupting renal blood flow, damaging compartments along the nephron, and obstructing urinary flow. A previous study has reported increased serum creatinine due to decreased clearance and glomerular filtration rate by lemon grass infusion, a phenomenon common to muscle kidney disease (Ekpenyong *et al*., 2014). Similarly, in this study, serum levels of creatinine of all rats treated with '*Shake'* herbal concoction were elevated when compared to the control ($p<0.05$). Thus '*Shake'* herbal concoction carries a high risk of causing damage to the liver.

Histopathological examinations of the brain at all doses (100, 200 and 400 $mgkg^{-1}$) of '*Shake'* showed regular neurons surrounded by oligodentrocytes, microglia and astrocytes across groups with no pathology seen. Thus, exposure of rats to '*Shake*' over an elongated period of time has no neurotoxic effect. Similarly, photomicrographs of the liver and kidney tissues showed normal organ architecture with no pathology seen.

V. CONCLUSION

Results obtained at the end of this study gave an insight as to the relative toxicity of '*Shake'* herbal snuff. Acute toxicity study outcome revealed that the drug is unlikely to cause fatal acute poisoning. However, sub-acute toxicity reports showed that it is capable of causing anemia by decreasing RBC, HGB, and HCT levels. This outcome, in view of a corresponding increase in white blood cells observed, could translate into a state of compromise immunity and consequently, increased risk of infection. Furthermore, increased creatinine level seen indicates a possible injury to the kidney. In conclusion, the oral use of '*Shake'* herbal snuff carries a potential for serious damage to the body.

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