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Safety Evaluation of *Picralima nitida* (Akuamma) Seed Extracton Hepatorenal and Haematological Systems of Rats

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ABSTRACT

Background: Plants like herbs has been extensively used for different kinds of nutritional and medicinal purposes, however, scientific studies has shown that these medicinal plants may have deleterious effects on some vital organs of the body if not taken at the recommended doses. Thus, there is a need for safety evaluation of these plants to ascertain their actions on organ's physiological functions. This present study evaluates the effects of ethanol seed extract of *Picralima nitida* on the haematological examines and some enzymes activities in the serum of albino rats. Twenty-five rats were equally randomized into five groups. Group A (control) received distilled water while graded doses (50, 100, 150 and 200 mg/kg body weight) of ethanol seed extract of *Picralima nitida* were administered to rats in groups B, C, D and E respectively for 14 days. Haematological studies were carried out on the rats' blood samples while concentrations of total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, and creatinine were measured in the serum.

Results: Result obtained revealed that treatment of rats with various graded doses of ethanol seed extract of *Picralima nitida* caused marked increase in urea and creatine compared to the control. Rats treated with 150 and 200mg/kg bw of the extract showed marked elevation in serum levels of the enzymes suggesting that the extract may have adverse effects at this dose. There was also a marked elevation in serum electrolytes of rats treated with 150 and 200mg/kg bw of the extract. Rats treated with low concentrations (50 and 100 mg/kg bw) of the extract demonstrated no marked differences or alteration in haematological parameters, protein profile and enzyme activities in the serum.

Conclusion: The results of this study indicated that consumption of ethanol seed extract of *Picralima nitida* as a therapeutic treatment is nontoxic at lower dose. However, if taken at high doses, the extract might be detrimental to some vital organs and systems.

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Abbreviations
ALT: Alanine aminotransferase
AST: Aspartate aminotransferase
Hb: Haemoglobin concentration
PCV: Packed cell volume
WBC: White blood cell count
RBC: Red blood cell count
MCHC: Mean cell haemoglobin concentration
MCV: Mean cell volume
ECV: Extracellular volume
PV: Plasma volume

Introduction

There is growing awareness and research focus on potential medicinal significances of naturally occurring phytochemicals and natural products from plants. Plants like herbs has been extensively used for different kinds of nutritional and medicinal purposes. Medicinal herbs have been in used for therapeutic purposes for decades prior to the establishment of traditional medicine. Roots, seeds, fruits, bark, flowers, stems, and leaves had been used as ingredients of herbal medications. The therapeutic importance of these part of plants or whole plants depends in their constituent secondary metabolites, which generate significant physiological effects on the human body. These medicinal herbs constituted the major reservoir for both orthodox and modern medicine [1].

Secondary metabolites of these medicinal plants are naturally occurring active compounds which are also known as phytochemicals. They possess prospective disease ameliorating proficiencies. Well known fact is that phytochemicals may be useful in fighting or preventing diseases due to their free radical scavenging, cytoprotective and antioxidant effects [2, 3]. Different studies on various plants extracts show they exerted their medicinal potentials via multiple pharmacological targets which is crucial in intensifying the health beneficial efficacy of bioactive agents present in these plants [4]. Antioxidants are substance that inhibit or slowdown the oxidation of other molecules (in vivo) when they

are attacked by free radicals and reactive oxygen species. This is an important factor in the aetiology and pathogenesis of many human diseases and in loss of quality of food and spoilage [5-7].

Phytochemicals have also been reported to exhibit considerable antioxidant activity [8]. Of particular therapeutic significance is polyphenolics which play crucialtask as antioxidants in the cytoprotective activities of homeopathic plants against various debilitating ailments and have become the target of novel prophylactic and pharmacological interest [9]. Antioxidant moleculessuch as flavonoids, polyphenols and phenolic acids have been documented to mitigate and scavenge free radicals like hydroperoxide of lipid hydroxyl, peroxide, and thus suppress the oxidative mechanisms involved in the progression of hepatotoxicity and nephrotoxicity in cells [10]. These phytochemicals have been demonstrated to have access to metabolic processes with a capacity to checkmate free radical-mediated biotransformation reactions by donating hydrogen from the phenolic hydroxyl groups to free radicalspecies [11].

Picralima nitida is a medicinal tree which has been used extensively in folklore medicine especially in Nigeria and other parts of West Africa. The seeds of *Picralima nitida* have been employed in the treatment of malaria, used as analgesic in pain management and as prophylactics in diarrhoea treatment [12]. These seeds comprise a combination of alkaloids such as akuammine, pericine and others which have been documented in scientific animal studies to have ability to reduce fever and pains with anti-inflammatory effects [13,14]. Many traditionalists have averred that various parts *Picralima nitida* tree has been effective in the treatment of various diseases such malaria, hypertension, and gastro-intestinal disorders [15]. Furthermore, seeds and stem of this plant have been documented to be a promising drug candidate in the treatment of cough, diabetes, hypoglycaemia and reproductive related diseases [16]. In view of the widespread use of *Picralima nitida* in traditional medicine, this study thus focused on exploring the possible deleterious effects of ethanol seed extract of *Picralima nitida* on some selected essential organs in rats.

Materials and methods

Chemicals/Reagents

Potassium ion, Sodium ion, Bicarbonate Concentration, Alanine aminotransferase (ALT), aspartate aminotransferase (AST), Urea, creatinine kits were products from Randox Laboratories Limited, United Kingdom. Ethanol, and other reagents used in this study were obtained from BDH Limited, Poole England and were of analytical grade.

Plant Material Collection and Preparation of Extracts

Fresh samples of *Picralima nitida* seeds were obtained in a garden located at Oke Baale Area, Osogbo, Nigeria. The authentication of the samples was done in the Biology Department of Federal University of Technology, Akure, Nigeria where a voucher specimen was deposited. The samples were allowed to dry at room temperature to constant weight and subsequently pulverized into powder. Thereafter, the sample was cold-macerated with 6 volumes of 80% ethanol for 72 hours. The mixture obtained was filtered and the filtrate concentrated at 80 °C using rotary evaporator. The paste obtained was weighed and reconstituted in water for subsequent studies.

Animals

Twenty-five Wistar strain albino rats weighing between 130–150g used for this study. They were sourced and raised at the breeding colony of of the Central Animal House, Osun State University, Osogbo, Nigeria. Animals were kept under ambient standard conditions (25 ± 2 °C and relative humidity of 50 ± 15 %) in stainless steel cages and metabolic wastes were cleaned twice daily. The rats were allowed to acclimatize to these conditions for fourteen days and were exposed to 12 hrs daylight and darkness cycle, fed with commercially available rat pellet and water ad libitum. This study conform to the NIH guide for the use and care of laboratory animals and the study was approved by the Institution's Ethical Committee.

Experimental Design and Dose Regimen

The animals were randomized into five (5) groups containing five (5) rats each. Group A (control) received distilled water orally while groups B, C, D and E were treated with different graded doses of *Picralima nitida* leaf extract (50, 100, 150, and 200 mg/kg bw respectively) for two weeks.

Blood collection and Preparation of Serum

The rats were sacrificed 24 hrs after the last dose has been administered by euthanized using chloroform. The blood samples were collected via direct heart puncture into sterile dry centrifuge tube. These blood samples were allowed to cloth at room temperature for 10 min and then spinned at 4,000 rpm in an MSC (Essex, UK) bench centrifuge. The clear supernatant (serum) was transferred into clean dry sample bottles aspirated Pasteur pipette and then stored at -4 for further analyses.

Estimation of Biochemical Parameters

Serum concentration levels of Potassium ion, Sodium ion, Bicarbonate Concentration, ALT, AST, Urea, creatinine in experimental rats were determined using the appropriate commercially available kits and method described by the manufacturer (Randox Laboratory Ltd, UK). Colometric assessment of protein concentration was carried out using bovine serum albumin as standard while the method described by Mokady was used to measure serum level of globulin. Albumin concentration in the serum was determined by following the protocol of the bromocrecsol green method [17-19].

Assessment of Haematological parameters

Haematological markers such as haemoglobin concentration (Hb), packed cell volume (PCV), white blood cell count (WBC), red blood cell count (RBC), mean cell haemoglobin concentration (MCHC), lymphocyte, mean cell volume (MCV), platelet counts and reticulocyte count were determined by using the automated multiparameter blood analyzer SYSMEX KX21 as earlier described Dacie and Lewis [20]. Briefly, 50 microlitres of blood samples were introduced into the equipment and it automatically employ the differences in characteristics possessed by each of the blood components to distinguish and estimate them [10].

Statistical Analysis

Results obtained were expressed as mean ± standard deviation (mean ± SD) and analysed using one-way analysis of variance (ANOVA) with the aid of SPSS 22.0 computer software package (SPSS Inc; Chicago, U.S.A) to compare the experimental groups followed by Bonferroni's post-hoc test. Valves at $P<0.05$ were considered significant.

Results and Discussion

Plants has been proven to be an important source of natural antioxidant and phytochemicals that mitigated oxidative stress instigated by an increase in free radicals/ROS and help in the treatment of many human diseases.Figure 1 shows that there is a marked increase ($P<0.05$) in the serum level of the electrolytes

(potassium, bicarbonate and sodium ions) in rats treated with higher doses of ethanol extract of *Picralima nitida* seed(150 and 200 mg/kg bw) compared with the untreated group. However, the observed increase in the lower concentrations of the extract (50 and 100 mg/kg bw) were not statistically significant.

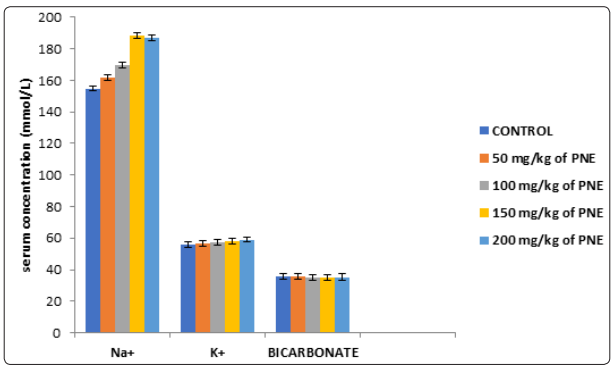


Figure 1: Effect of various concentrations of ethanol extract of *Picralima nitida* seed on serum electrolytes in rats.

Data are given as mean ± SD of rats per group. PNE: ethanol extract of *Picralima nitida* seed, Na+: Sodium ion, K+: Potassium ion

Sodium ion (Na^+) is an essential ion needed for generation of action potentials in nervous and cardiac tissue, thus, the principal extracellular cation/solute. Pathologic increases or decreases in total body Na^+ are associated with corresponding increases or decreases in extracellular volume (ECV) and plasma volume (PV) while Potassium is the major intracellular cation. It helps to establish the resting membrane potential in neurons and muscle fibres after membrane depolarization and action potentials [21]. Furthermore, the increase in the ions observed in rats treated with higher doses in this study may be as a result of excessive extracellular sodium ion relative to water which is characterized by decrease in body water and increase in body sodium ion and also with the increase in the K+ concentration may be as a result of kidney failure or by the sudden release of potassium ion from the intracellular compartment as a results of several diseases. [22, 23].

In clinical practice, serum electrolytes (potassium, sodium, and bicarbonate ions) are amongst biomarkers measured routinely in the assessment of renal functions [24]. Increase or reduction in serum level of these electrolytes may be an indication of renal disorder in response to which clinical check-up for kidney function is necessary. But in some pathological conditions such as diarrhoea, these serum ions are vanished in the fluids and in the case of excessive intake of these electrolytes or dehydration these ions concentration increase and balance in them may be disrupted [25].

Results of the kidney metabolites studied in this study was revealed in Figure 2. At lower treatments (50 and 100 mg/kg bw), there is no marked changes in the serum level of urea and creatine when compared with the untreated group. However, there was a marked increase ($P<0.05$) in the serum level of urea and creatine in groups treated with 150 and 200 mg/kg bw of ethanol extract of *Picralima nitida* seed compared with the untreated group. The observed increase in serum levels of urea and creatine after fourteen days of treatment with 150 and 200 mg/kg bw of ethanol extract of *Picralima nitida* seed may be as a result of leakage of kidney membrane and excessive protein intake [26]. Similarly, the elevation in serum level of creatinine and urea maybe as a result of impairment in kidney function as previously documented that significant creatinine retention in the blood is evidence of kidney impairment [27].

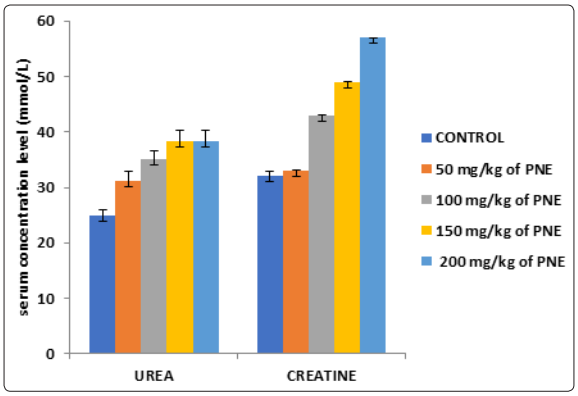


Figure 2: Effect of various concentrations of ethanol extract of *Picralima nitida* seed on kidney metabolites (urea and creatine) in rats.

Data are given as mean ± SD of rats per group. PNE: ethanol extract of *Picralima nitida* seed.

Figure 3 reveals the results of serum level of globulin, albumin and total protein in the experimental rats. The data shows that there is no marked changes ($P<0.05$) in the serum level of proteins in rats treated with various doses of ethanol extract of *Picralima nitida* seed (50, 100, 150 and 200 mg/kg bw) compared with the untreated group. There are scientific evidences that some herbal mixtures have hepatotoxic and nephrotoxic effects [28, 29]. The loss of reliability and functionality of these homeostatic organs (liver and kidney) would definitely lead to the increase of serum protein profile like serum protein, globulin and albumin. A marked level of the serum protein, globulin and albumin within the reference range which are markers of cellular damage post 14 days oral administration of the seed extract of picralima nitida at the higher concentrations (150 and 200 mg/kg bw) were observed in the course of the study.

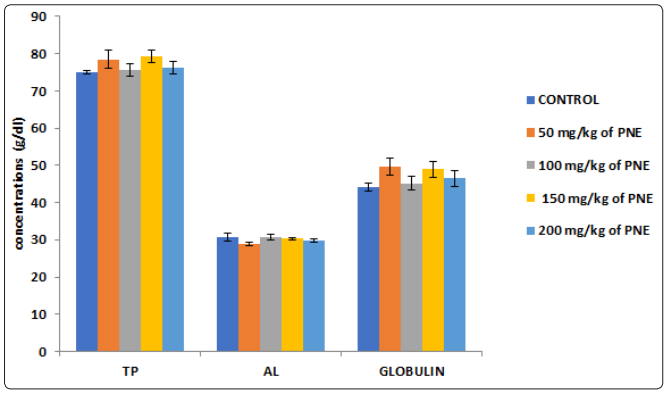


Figure 3: Effect of various concentrations of ethanol extract of *Picralima nitida* seed on serum protein profile in rats.

Data are given as mean ± SD of rats per group. PNE:ethanol extract of *Picralima nitida* seed, TP: Total protein, AL: Albumin

Figure 4 shows that there is a marked increase in the serum level of aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) in rats treated with higher doses of ethanol extract of *Picralima nitida* seed (150 and 200 mg/kg bw) compared with the untreated group. However, the observed increase in the lower treatments of the extract (50 and 100 mg/kg bw) were not statistically significant. The biochemical studies of ALT and AST in this study show a dose and time dependent significant

($p<0.05$) elevation in the serum and it has been established that hepatocellular injury leading to permeability of intracellular enzymes into the bloodstream is accompanied by elevated ALT and AST [30, 31].

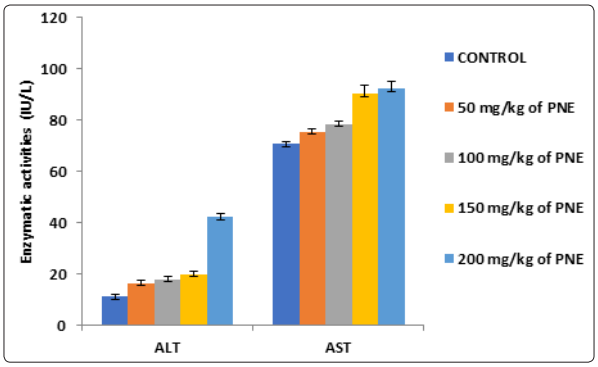
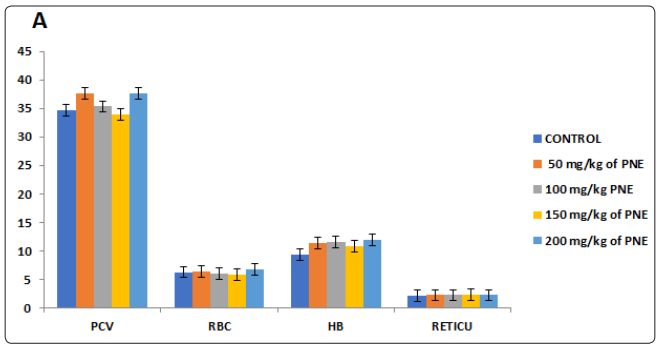
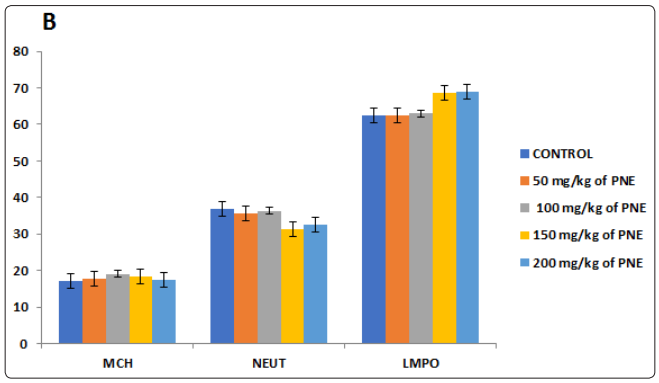


Figure 4: Effect of various concentrations of ethanol extract of *Picralima nitida* seed on serum hepatic markers (ALT and AST) in rats.

Data are given as mean ± SD of rats per group. PNE: ethanol extract of *Picralima nitida* seed.

Results of the haematological studies on the experimental rats used in this was depicted in Figure 5 A, B and C. The data shows that there is no marked changes in level of RBC (red blood cell count), RETICU (reticulocyte) and MCH (mean capsulated haemoglobin) in rats treated with 50, 100, and 150 mg/kg bw of ethanol extract of *Picralima nitida* seed compared with the untreated group. However, rats treated with 200 mg/kg body weight of the extract shows a marked increase in pack cell volume (PCV), haemoglobin concentration (HB), Lymphocyte (LMPO) and platelet when compared with the control. The haematological studies reveal that administration of various concentrations of the extract cause increase in all the haematological parameters. These results suggested that the extract has immunostimulant potentials.





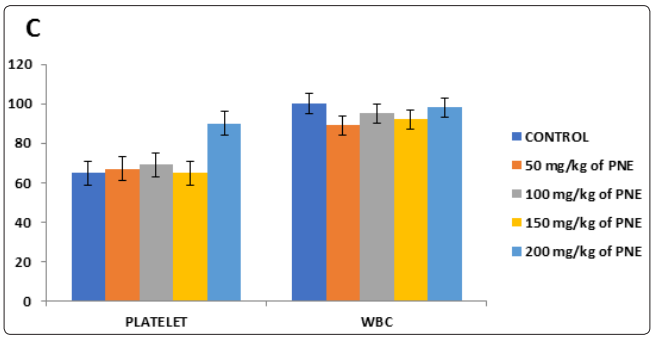


Figure 5: Effect of various concentrations of ethanol extract of *Picralima nitida* seed on haematological parameters in experimental rats.

Data are given as mean ± SD of rats per group. PNE: ethanol extract of *Picralima nitida* seed. PCV: Pack cell volume (%), HB: Hemoglobin concentration (g/dl), RBC: Red blood cell count ($\times 10^6$ µl), WBC: White blood cell count ($\times 10^3$ µl), LMPO: Lymphocyte (%), PLT: Platelets ($\times 104$ µl), MCH: Mean capsulated haemoglobin (g/dl).

Figure 6 shows that there is a marked elevation in the level of total and direct bilirubin in rats treated with higher doses of ethanol extract of *Picralima nitida* seed (150 and 200 mg/kg bw) compared with the untreated group. However, the observed increase in the lower concentrations of the extract (50 and 100 mg/kg bw) were not statistically significant. An increase in bilirubin concentration in serum is called jaundice. 50 and 100 mg/kg bw administration of the extract shows no marked increase in concentration of direct bilirubin compared with the untreated group while there was a significant increase in the concentration of direct bilirubin in group 150 and 200 mg/kg bw ($p< 0.05$) when compared with the untreated group. This observed increase in the direct bilirubin concentration may be due to haemolytic jaundice due to presence of high content of saponin in the extract, drug induced reaction and bile not being properly excreted which can be as a result of an obstruction in the bile duct or gall bladder [32].

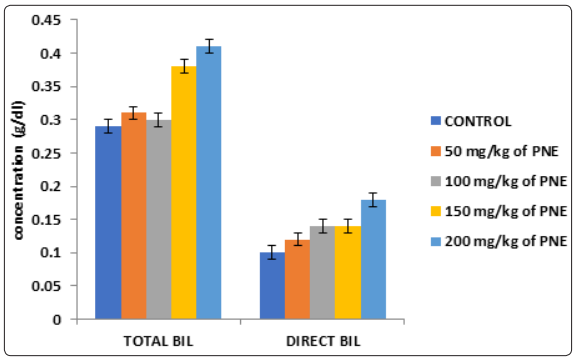


Figure 6: Effect of various concentrations of ethanol extract of *Picralima nitida* seed on total and direct bilirubin in experimental rats.

Data are given as mean ± SD of rats per group. PNE: ethanol extract of *Picralima nitida* seed. Bil: Bilirubin

Conclusion

Taken together, the result obtained in this present study indicated that intake of graded doses of ethanol seed extract of *Picralima nitida* can improve haematological parameter in animals. Intake of *Picralima nitida* seed as medical intervention in the treatment of diseases at low concentration has no deleterious consequences

on the hepatic and renal system but the extract might have adverse effects on the organs if used at high doses.

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Authors' Contributions
OMO and OJO conceived the study, and participated in its design and execution and helped to draft the manuscript; OBD participated in the execution of the study; OMO participated in the design, coordination and helped to draft the manuscript; OTO participated in the execution of the study; All authors read and approved the final manuscript.

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Availability of data and materials
Please contact corresponding author for data requests.

Ethics approval and consent to participate
All experimental procedures were approved by the Institutional AnimalEthics Committee.

Consent for publication
All the authors contributed, agreed, submitted, and revised thismanuscript.

Competing interests
The authors declare that they have no competing interests.

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