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Nephrotoxicity Assessment of Dr Iguedo Goko Cleanser® in Exposed Wistar Rats

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Authors' contributions

This work was carried out in collaboration among all authors. Authors GJU, JEO and JAU designed the work. Author GJU wrote the protocol and first draft of the manuscript. Authors JEO and JAU reviewed and vetted the first draft. Author DNO managed the literature searches and effected corrections to the first draft. Author GJU performed the statistical analysis and managed the analytical cost of the study. Author IEA eviscerated the kidney tissues from the euthanized experimental rats. All authors read and approved the final manuscript.

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ABSTRACT

Aims: This study was designed to evaluate the toxicity concern of Dr Iguedo Goko Cleanser® on kidney function parameters and histoarchitecture of the kidneys of exposed Wistar rats.
Study Design: A 60-day subchronic toxicological assessment using animal model.
Place and Duration of Study: Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Uyo, Nigeria, between March 2019 and July 2019.

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Methodology: Acute toxicity study was conducted using the modified Lorke's method. Thirty Wistar rats of both genders were randomly allotted to six groups (5/group) and orally-treated daily thus: Groups 1 and 4-Controls (distilled water, 10 mL/kg), Groups 2-3; 5-6 received the Polyherbal mixture (476.24; 158.75) mg/kg, respectively. On 62nd day, animals were euthanized under diethyl ether anaesthesia and sacrificed. Blood samples were collected by cardiac puncture for biochemical analysis. Eviscerated kidneys were weighed and fixed in 10% formalin for histopathological examination.

Results: Polyherbal mixture presented acute toxicity with an estimated LD_{50} of 1587.45 mg/kg (mouse, i.p). Results presented significant (*P*=.05) decreased blood urea nitrogen at all doses tested; elevated Na^+ for high dose male (124.58±1.82) and female (122.77±0.00) rats compared to their respective controls (110.49±3.17/97.33±1.78) as well as increased creatinine levels for low dose male rats (145.83±7.45) compared to control (36.46±1.24). Histopathology of the kidneys revealed degrees of pathologies such as hyperplasic glomerular cells, occluding Bowman's space, hyperaemia within the cortical tissue, widened proximal and distal convoluted tubules, hyperplasia of cortical tissue cells as well as hyperplasia of tubular and connective tissue cells.

Conclusion: Despite the popular claim that herbal remedies are completely natural, safe and devoid of toxicities whatsoever, the present day study suggest otherwise. Therefore, utmost caution and/or avoidance of the polyherbal mixture whenever possible, is strongly advised especially as its nephrotoxic potentials are not negligible.

Keywords: Nephrotoxicity; herbal remedies; kidney; glomerulus; hyperplasia.

1. INTRODUCTION

Presently, self-medication is a common practice in the Nigerian state and there is an upsurge in the circulation of various kinds of drugs and quasi-drug formulations [1], many of which are allegedly licensed by the National Agency for Food Drug Administration and Control (NAFDAC). In most countries of the world but predominantly in Africa and Asia, herbal medicines and their derivatives (unfinished and finished/labelled products) are introduced into the market without any mandatory safety or toxicological evaluation [2]. Many of these countries also lack effective machinery to regulate manufacturing practices and quality standards. These herbal products are continuously made available to consumers without prescription in most cases and the potential hazards in an inferior product are hardly recognized [2]. Due to failure in standardization, most of these preparations may be contaminated with heavy metals, polycyclic aromatic hydrocarbons (PAHs) as well as other chemicals and/or may contain impurities that put humans at risk. Thus, exposures to these everyday items are of serious concern to public health. Dr Iguedo Goko Cleanser® is a polyherbal mixture with NAFDAC registration number, A7-0804L, and is claimed to cure well over 50 different diseases. Its contents are made of five different plants and a flavouring/colouring agent as shown: *Vernonia amygdalina* (bitter leaf), *Cajanus cajan* (pigeon pea), *Zingiber officinale* (ginger), *Allium sativum* (garlic), *Saccharum officinarum* (sugar cane) and caramel. Herbs and their derivatives have been shown to be capable of producing a wide range of undesirable or adverse reactions some of which are capable of causing serious injuries, life-threatening conditions, and even death. Numerous and irrefutable cases of poisoning associated with herbal remedies have been reported in the literature [3-5].

Concomitant use of conventional and herbal medicines is commonplace in the Nigerian state. Such practices are not without consequences especially as most patients who earlier presented to hospitals but absconded to patronize herbal remedies tend to return at a later stage with end-stage and multiple organ complications and in most cases, mortality ensues. Owing its pivotal role in metabolism and excretion of xenobiotics as well as homeostasis, the kidneys may be compromised by inadvertent and/or indiscriminate exposure to certain substances (including herbal remedies). End stage renal disease occurs when the gradual loss of kidney function (chronic kidney disease) reaches its advanced state. It is multifactorial and is often reported in patients who abscond from hospitals to patronize herbal drugs and other quasi-drug formulations. It was estimated to be the 12th most common cause of death with a global death toll of about 1.1 million [6,7]. Over the last decade, CKD has recorded a 37.7% increase, placing it as one of the fastest causes of death [6]. Therefore, the prevalence of kidney disorders

as well as the increasing evidence of adverse effects related to herbal medicine further highlights the demand and necessity for toxicological evaluations of these substances that freely circulate in the Nigerian market. Therefore, this research was designed to determine the nephrotoxicity profile of the polyherbal mixture (Dr Iguedo Goko Cleanser®) using suitable experimental models. Such findings if and when communicated effectively (after interspecies' extrapolation), will help protect public health against exposure-associated adverse health effects.

2. MATERIALS AND METHODS

2.1 Preparation of Stock Solution and Calculation of Dose

The test samples were purchased from a major distributor in Uyo metropolis. Aliquots (5 mL) of the polyherbal mixture was measured into five weighed empty beakers and evaporated to dryness using a hot plate (Griffin, Britain) and the marc was determined. The stock concentration was determined by taking the average of the differences between the weight of the beakers and weight of marc in 5 mL of the solution (test sample) using the procedure below:

Weight of beaker = A (g)
Weight of beaker + marc = B (g)
Weight of marc = B – A (g)
Concentration of drug used (mL) = X g/mL = ∑B – A (g) / N

The final doses administered in mL were calculated using the formula:

$$Dose\ [mL] = \frac{Weight\ of\ Animal\ [kg] \times Dose\ [mg/kg]}{Stock\ concentration\ [mg/mL]}$$

2.2 Experimental Animals

The animals (Swiss albino mice and Wistar albino rats of both genders) were obtained from and kept at the Department of Pharmacology & Toxicology Animal House of the Faculty of Pharmacy, University of Uyo, Uyo, Nigeria. The animals were maintained under standard environmental conditions and fed with standard Pfizer-branded rodent feed (Livestock Feed, Nigeria Ltd) and given access to water *ad libitum*. All animals were kept at room temperature in cross-ventilated rooms, without illumination at night to achieve the 12 h light/ 12 h dark period. The animals were acclimatized to the laboratory condition for at least 7 days prior to the experiment, during which they were given access to food and water *ad libitum*.

2.3 Acute Toxicity Test

The median lethal dose (LD_{50}) of the polyherbal mixture was determined intraperitoneally (ip) according to the modified method of Lorke [8] using Swiss albino mice (16 – 27 g; n = 18) fasted overnight. The animals were divided into six groups of three animals per group and administered intraperitoneally varying doses of the polyherbal mixture as shown in Table 1.

The animals were observed for cardinal signs of toxicity and mortality within 24 h. The estimated LD_{50} was used to select the appropriate doses to be administered during the 60-day subchronic toxicity studies. The LD_{50} was calculated using the formula:

$$LD_{50} = \sqrt{AB}$$

Where

A = maximum dose with 0% mortality and
B = minimum dose with 100% mortality.

2.4 Experimental Design

A total of 30 adult Wistar rats of both genders (15 each) were weighed and randomly allotted to six groups of five animals each and treated as shown in Table 2.

The doses were administered daily using oral gavage for 60 days of the test period [9,10]. Rats in different groups were observed closely for any behavioural changes, feeding and drinking habits, as well as body weight and general morphological changes. After the test period, the animals were euthanized under diethyl ether (Sigma, USA) anaesthesia and sacrificed. Blood samples were collected through cardiac puncture into plain sample bottles for biochemical (creatinine, blood urea nitrogen and serum electrolytes) investigations. The kidneys were eviscerated for internal macroscopic and histopathological examinations.

2.5 Biochemical Analysis

Using a centrifuge (Nikon optical Co., Japan), whole blood of each sacrificed rat collected through cardiac puncture into different plain sample bottles were centrifuged at 2500 rpm for 20 min at 10°C to obtain the serum. Serum urea

Table 1. Experimental design for acute toxicity testing of the polyherbal mixture

S/N	Treatment	Dosage (mg/kg)	Observed duration
1	Group 1	1000	24 h
2	Group 2	1200	24 h
3	Group 3	1400	24 h
4	Group 4	1600	24 h
5	Group 5	1800	24 h
6	Group 6	2000	24 h

Table 2. Experimental design

S/N	Treatment group	Dosage	Duration
1	CM	10 mL/kg DW	60 days
2	HDM	476.24 mg/kg GC	60 days
3	LDM	158.75 mg/kg GC	60 days
4	CF	10 mL/kg DW	60 days
5	HDF	476.24 mg/kg GC	60 days
6	LDF	158.75 mg/kg GC	60 days

DW = Distilled water, GC = Goko Cleanser, CM = Control males, HDM = High dose males, LDM = Low dose males, CF = Control females, HDF = High dose females, LDF = Low dose females

level was measured using the couple urease/glutamate dehydrogenase (GLDH) enzyme [11]. Serum creatinine (SCr) was assayed based on the reaction of creatinine with an alkaline solution of sodium picrate to form a red complex [12]. Serum electrolytes levels were determined using standard methods. Serum creatinine and blood urea nitrogen (BUN) levels were measured as markers of kidney function. Except otherwise stated, all biochemical investigations were done using automated analysers and Fortress Diagnostic Kits® (Fortress Diagnostic Limited, UK) according to standard procedures of manufacturer's protocols at Bridge Bio-Tech Ltd, Ilorin.

2.6 Histopathological Assessment

After the collection of blood from the diethyl ether euthanized and sacrificed rats, the kidneys were immediately excised, freed from adventitia, blotted with tissue paper, weighed, sectioned and fixed in 10% formalin for histological studies. The fixed sections were passed through xylene, alcohol and water to ensure that the tissues were totally free of wax and alcohol. Each section was then stained with haematoxylin and eosin for photo-microscopic assessment using light microscope at a magnification of 400. To minimize bias, the pathologist was denied knowledge of the doses and treatments given to the different groups of experimental rats [13].

2.7 Statistical Analysis

Data generated was statistically analysed using SPSS version 17. Statistical significance between the groups were analysed by means of one-way analysis of variance (ANOVA). Results were presented as Mean ± S.E.M. and values less than (P= .05) were considered significant.

2.8 Limitations

The study was not followed by a 14-day reversibility study (where exposure of the lower animals to the polyherbal mixture must have been discontinued and all parameters determined in the main work repeated) due to set limits.

3. RESULTS

3.1 Acute Toxicity Test

The result of this test is presented in Table 3. From the result, 100% and 0% mortality were respectively recorded at 1800 – 2000 and 1000 – 1400mg/kg body weight of the herbal mixture. At the dose levels tested, cardinal signs of toxicity observed were decreased motor function and somnolence. There were no changes in the nature of stool, urine and eye colour in all the surviving mice. This suggests that the herbal mixture may possess some central nervous system inhibitory properties. The LD_{50} value of the herbal mixture was estimated to be 1587.45 mg/kg body weight (mouse, i.p).

Table 3. Acute toxicity test result of Dr Iguedo Goko Cleanser®*

Test groups	Dose (mg/kg)	Fraction of death	% Mortality
1	2000	3/3	100
2	1800	3/3	100
3	1600	2/3	67
4	1400	0/3	0
5	1200	0/3	0
6	1000	0/3	0

Route of administration: Intraperitoneally; n = 18

3.2 Kidney Function Parameters

Results for electrolytes, urea and creatinine (EUC) assay presented no significant differences in the concentration of the bicarbonate ions in both experimental male and female rats relative to their respective control groups as well as comparison between different groups. Similarly, there were no significant differences in the concentration of the potassium ions in both experimental male and female rats relative to their respective control groups. However, the control females had significantly (*P*= .05) low serum potassium ions compared to low dose males. There was no significant difference in serum chloride ion concentration in the experimental male and female rats compared to their respective controls. However, the low dose females had significantly low serum chloride ions compared to the high dose males.

The serum concentration of sodium ions was significantly elevated in the high dose males (124.58 ± 1.82) but decreased in low dose male rats (84.10 ± 1.57) compared to control males (110.49 ± 3.17). Also, significant increases were recorded for the experimental female rats (122.77 ± 0.00; 145.32 ± 0.00) in comparison to control (97.33 ± 1.78). High dose female rats (122.77 ± 0.00) had increased serum Na^+ compared to control and low dose male rats (110.49 ± 3.17; 84.10 ± 1.57), while low dose female rats (145.32 ± 0.00) had significantly increased serum Na^+ in comparison to the experimental male rats as well as the control (97.33 ± 1.78) and high dose female rats (122.77 ± 0.00) respectively (Fig. 1).

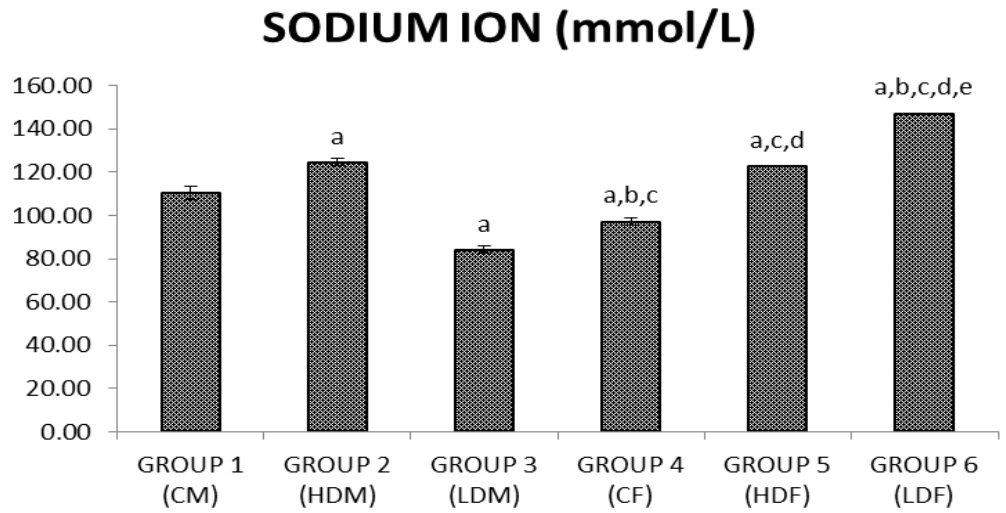

Fig. 1. Serum sodium levels of wistar rats exposed to Dr Iguedo Goko Cleanser®

Data presented as Mean ± Standard Error of Mean (SEM). Compared means are considered statistically significant at P=.05; a = significantly different when compared to CM (control males); b = significantly different when compared to HDM (high dose males); c = significantly different when compared to LDM (low dose males); d = significantly different when compared to CF (control females); e = significantly different when compared to HDF (high dose females); n = 5

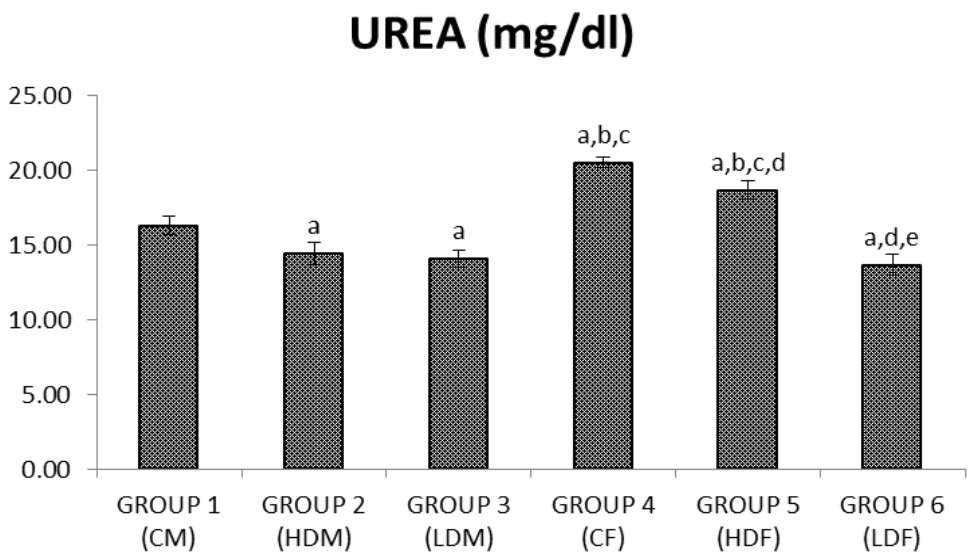

Fig. 2. Serum urea levels of wistar rats exposed to Dr Iguedo Goko Cleanser®

Data presented as Mean ± Standard Error of Mean (SEM). Compared means are considered statistically significant at P=.05; a = significantly different when compared to CM (control males); b = significantly different when compared to HDM (high dose males); c = significantly different when compared to LDM (low dose males); d = significantly different when compared to CF (control females); e = significantly different when compared to HDF (high dose females); n = 5

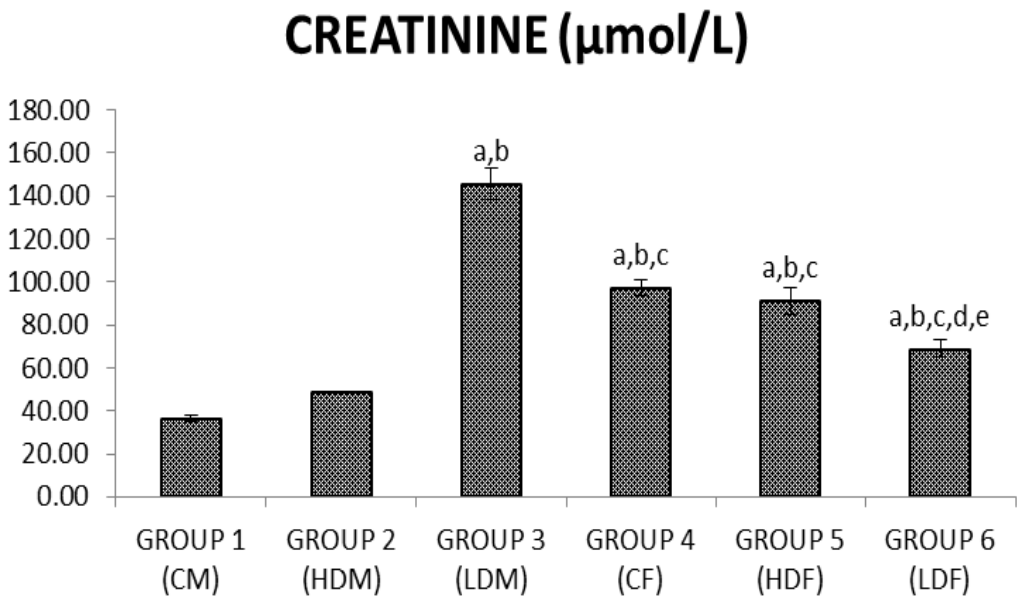

Fig. 3. Serum creatinine levels of Wistar rats exposed to Dr Iguedo Goko Cleanser®

Data presented as Mean ± Standard Error of Mean (SEM). Compared means are considered statistically significant at P=.05; a = significantly different when compared to CM (control males); b = significantly different when compared to HDM (high dose males); c = significantly different when compared to LDM (low dose males); d = significantly different when compared to CF (control females); e = significantly different when compared to HDF (high dose females); n = 5

There were significant reductions in blood urea nitrogen in both high dose (14.44 ± 0.73) and low dose male (14.09 ± 0.60) rats relative to their control (16.28 ± 0.62). Similarly, there was a significant dose dependent decrease in urea in the experimental female rats (18.69 ± 0.59; 13.68 ± 0.68) in comparison to their control (20.52 ± 0.35). Female rats (CF and HDF only) had higher urea levels compared to the male rats (Fig. 2). Significant increase in creatinine was recorded in the low dose male (145.83 ± 7.45) group in comparison to control (36.46 ± 1.24) and high dose male (48.61 ± 0.00) groups. The low dose females (68.87 ± 4.05) had significantly low creatinine level compared to control (97.22 ± 3.73) and high dose female (91.15 ± 6.08) as well as the low dose male (145.83 ± 7.45) groups. However, serum creatinine was higher in the low dose females in comparison to control and high dose male rats (Fig. 3).

3.3 Histopathological Assessment

Histological examination of the kidney of rats (both genders) in the control groups presented preserved and normal cellular architecture of renal cortex with the urinary tubule, proper orientation of layers of urinary ducts and well-spaced bowman capsule. However, high and low dose groups of experimental rats showed some degree of pathologies such as renal cortex with hyperplasic glomerular cells, degenerated glomerulus, occluding bowman space, widened bowman space, hyperaemia within cortical tissue, widened proximal and distal convoluted tubules, hyperplasia of cortical tissue cells as well as the hyperplasia of tubular and connective tissue cells (Fig. 4).

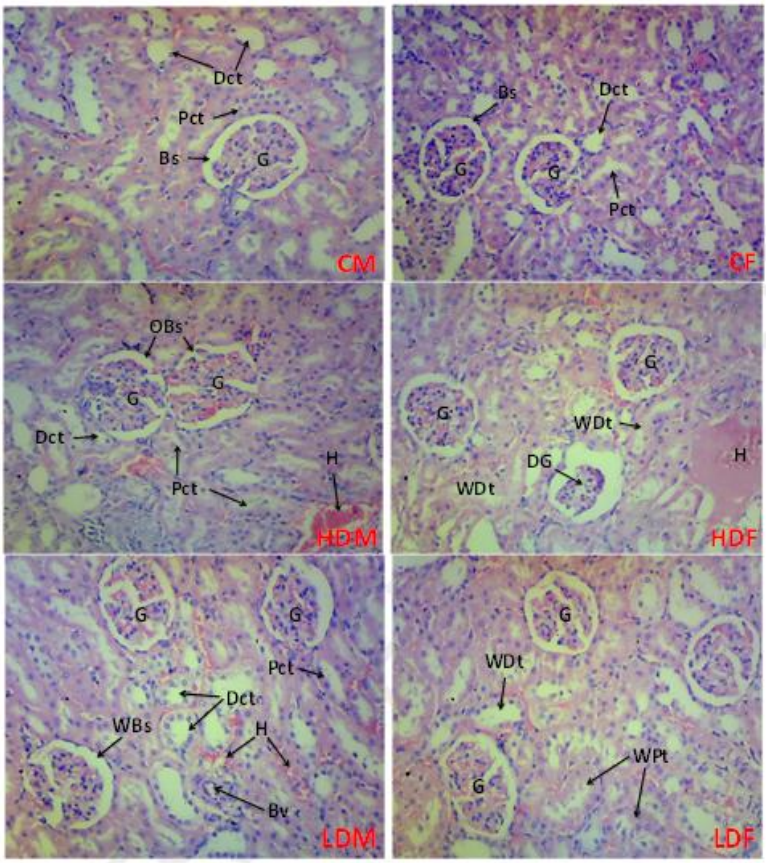

Fig. 4. Typical kidney sections from controls and Dr Iguedo Goko Cleanser® exposed wistar rats

CM = Control males, HDM = High dose males, LDM = Low dose males, CF = Control females, HDF = High dose females, LDF = Low dose females, OBs = Occluding Bowman space, H = Hyperaemia, WPt = Widened proximal tubules, Hp = Hyperplasia, WBs = Widened bowman space, Bv = Blood vessel, DG = Degenerating glomerulus, G = Glomerulus, Pct = Proximal convoluted tubule, Dct = Distal convoluted tubule x 100 magnification

4. DISCUSSION

Electrolytes and the balance thereof are vital for homeostasis and overall body physiology. For instance, both muscle tissue and neurons which are considered electric tissues of the body are activated by electrolyte activity between the extracellular fluid and intracellular fluid. This underscores the fact that for normal functioning of the cells and organs, a balance in electrolytes is needed between these fluid spaces of the body [14]. Muscle contraction is dependent on the presence electrolytes like sodium (Na^+), calcium (Ca^{2+}), and potassium (K^+), without sufficient levels of these key electrolytes, muscle weakness or severe muscle contractions may occur. Sodium is required for the generation and conduction of action potentials as well as contraction and relaxation of muscles. It regulates or maintains the proper balance of water and minerals in the body. The transmission of sodium in and out of individual cells plays a critical role in the body functions [15]. Too much or too little sodium therefore can cause cells to malfunction, and extremes in blood sodium levels (hypo or hyper) can lead to fatal conditions [15]. Excessive sodium can lead to or worsen existing pathological conditions like hypertension, heart disease and cerebrovascular accident. Evidence suggests that excess sodium can damage the aorta, heart and kidney without necessarily causing a shoot in blood pressure. As sodium accumulates, in most people, it becomes problematic for the kidneys to keep up with such excesses. Smyth et al. [16] reported that salt sensitivity is more prevalent in patients with CKD and this is due to the inability or reduced ability of the kidneys to excrete excess sodium ions. In this study, a decrease in water intake was observed in the experimental female rats. This may therefore explain the elevated serum sodium levels recorded in these groups of animals. Reduction in serum chloride below the clinically accepted range is indicative of dehydration and shock [14]. Thus, the recorded decrease in chloride ion in the low dose female rats suggests a possible dehydration. Though the exact mechanism of action cannot be established, the electrolyte imbalance observed in the experimental subjects recruited in this study is attributed to the subchronic exposure to the herbal drug, Dr Iguedo Goko Cleanser®.

Blood urea nitrogen (BUN) and serum creatinine are screening tests of renal function. This is because they are handled primarily by glomerular filtration with little or no renal regulation or adaptation in the course of declining renal function, rather, they essentially reflect glomerular filtration rate (GFR). Their values remain relatively normal until more than 50% of renal function is lost [17]. They are also used for the differential diagnosis of prerenal hyperuremia (cardiac decompensation, water depletion, and increased protein catabolism), renal hyperuremia (glomerulonephritis, chronic nephritis. polycystic kidney, nephrosclerosis, and tubular necrosis) and postrenal hyperuremia (obstructions of the urinary tract such as stones, enlarged prostate gland and tumours). Urea is the final degradation product of protein and amino acid metabolism. Significantly lower urea denotes acute tubular necrosis, low protein intake, starvation or severe liver disease. High ratios of BUN with normal creatinine may be noted with catabolic states of tissue breakdown, pre-renal azotemia and high intake of protein. Also, high ratios of BUN associated with high creatinine concentrations may denote either post-renal obstruction or pre-renal azotemia superimposed on renal disease [18]. Therefore, the significant reduction in BUN observed at all doses tested in comparison to the respective control groups may be indicative of a possible undesired effect of the herbal mixture, Dr Iguedo Goko Cleanser®.

Creatinine is a metabolite of muscle creatine, whose amount in serum is proportional to the body's muscle mass and body size, and this explains why creatinine levels are usually slightly elevated in males than females and children. It is a major catabolic product of the muscles and protein respectively. Serum creatinine is an important test for knowing the working condition of the kidneys. This is so as almost all creatinine is filtered from the blood by the kidneys and released into the urine. Elevated levels of serum creatinine indicate diminished renal function, as it is excreted by the kidney [19,20]. According to Adeyemi and Akinwande [21], elevated serum creatinine is clinical biomarker for muscular dystrophy or wasting disease. More so, significant increases in serum creatinine generally indicate diseases affecting the cardiac muscle. Secretion of creatinine occurs through a combination of glomerular filtration and tubular secretions. Therefore, elevated serum creatinine levels may be due to these two factors and could indicate renal damage [21]. In this study, a four and threefold increase in serum creatinine was recorded in male rats that received low dose of the herbal mixture in comparison to the control and high dose males respectively and this is

again attributed to exposure to Dr Iguedo Goko Cleanser®.

The nephron is the structural and functional unit of the kidney, and the glomerulus (an approximately 200 µm diameter structure), is formed by the invagination of a tuft of capillaries into the dilated, blind end of the nephron. Functionally, it is from the glomeruli that the filtrates are formed. Hence, the degeneration and hyperplasia of the glomerulus as shown by the histopathological examination of the kidneys is indicative of impaired glomerular functions, and is attributed to the repeated exposure to the polyherbal mixture. The Bowman capsule is a capsular structure that encloses the glomerulus. The functional anatomy of Bowman capsule resembles a funnel with filter paper. There exists a certain type of pressure in the Bowman's capsule that is one of the determinants of glomerular filtration. It is known as the hydrostatic pressure or capsular pressure**.** The pressure is exerted by the filtrate in Bowman capsule, and is known to oppose glomerular filtration because it is inversely proportional to the GFR. When the hydrostatic pressure increases in the Bowman capsule, it decreases GFR. Hydrostatic pressure in Bowman capsule increases in conditions like obstruction of urethra and oedema of kidney beneath renal capsule. It is inferred that there was an increased hydrostatic pressure in the Bowman's capsule due to the occlusion of its space as revealed by the histopathological assessment of the kidneys of the experimental subjects. Owing to its attendant effect on GFR and urine formation, it is thought that the function of the glomerulus was significantly hindered in these groups of animals.

The observed hyperaemia suggests vascular congestion, and usually accompanies renal ischemia with a characteristic cellular swelling in its generation. It has been proposed that the loss of interstitial and vascular fluid during ischemia is the cause of the vascular congestion, which, in turn, is responsible for the poor perfusion and impaired renal function seen after ischemia [22]. The inflammatory response may be implicated in renal injury as leukocytes infiltrate and cause oedema by compromising microvascular blood flow [23]. Congestion within peripheral vascular tissues, in addition to renal and cardiac tissues triggers local followed by systemic inflammatory responses which promote additional fluid retention when endogenous anti-oxidative, anti-inflammatory, and vasodilating defences are overwhelmed [24]. The observed hyperaemia or vascular congestion in the present study corroborates findings of Onyejike et al. [25], which revealed that Dr Iguedo Goko Cleanser® "dose-dependent toxic (haemorrhagic) effect on the kidney". Therefore, the kidneys are susceptible organs of concern in this subchronic toxicity test. However, reversibility study was not carried out to see whether or not there will be any reversal of test effect on exposure withdrawal or discontinuation.

5. CONCLUSION

Findings of this study reveal that Dr Iguedo Goko Cleanser® is relatively safe on acute oral exposure with an estimated LD_{50} of 1587.45 mg/kg body weight (mouse, i.p). It further highlights inherent abilities of the polyherbal mixture to induce an array of renal toxicities especially on long term use. Contrary to the popular belief that herbal drugs are 100% natural, completely safe and devoid of any toxicity whatsoever, the present study has revealed the nephrotoxic potentials of the polyherbal mixture such as hindered renal functions as well as distorted structural and cellular integrity of the kidneys in Wistar rats of both genders. Therefore, the chronic (intermittent, continuous) or long-term use of Dr Iguedo Goko Cleanser® should be done with utmost caution, and wherever possible, be avoided.

DISCLAIMER

The products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All necessary ethical considerations as regard the use of animals and humans in research were satisfactorily met. The care and use of animals was conducted in accordance with the National

Institute of Health Guide for the Use of Laboratory Animals (NIH, 1996). Moreover, ethical approval for animal use was obtained from the Experimental Ethics Committee on Animal Use of the Faculty of Pharmacy, University of Uyo, Nigeria.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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