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Hepatotoxicity Assessment of a Polyherbal Mixture in Exposed Wistar Rats

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Authors' contributions

This work was carried out in collaboration among all authors. Author GJU designed the research work, 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, while author NJO effected corrections to the first draft. Author GJU performed the statistical analysis. Author IEA eviscerated the liver tissues from all the euthanized experimental rats. All authors made significant financial contributions as well read and approved the final manuscript.

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ABSTRACT

The study evaluates the toxicity concern of a polyherbal mixture (Dr Iguedo Goko Cleanser®) on liver function parameters and liver histoarchitecture of exposed Wistar rats of both gender. Thirty (30) Wistar rats of both genders were randomly allotted to (6) six groups (5/group). Groups 1 and 4 were controls and received 10 mL/kg body weight of distilled water. Groups 2-3 and 5-6 received high (476.24 mg/kg) and low (158.75 mg/kg) doses of the polyherbal mixture respectively. On 62nd

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day, the animals were euthanized under diethyl ether anaesthesia and sacrificed. Blood samples were collected via cardiac puncture for biochemical analysis. From each animal, the liver was eviscerated, weighed and fixed in 10% buffered formalin for histopathological examination. Results presented a significant ($p<0.05$) increase in ALT activity for high dose female (HDF) rats; while a decrease was recorded for low dose male (LDM) rats. Significant reduction in AST activity was recorded for the male rats. Whereas, decreased and increased AST activities were respectively recorded for high and low dose female rats. ALP activities were significantly reduced and elevated in the exposed male and female rats respectively. The histopathology of the liver revealed degrees of pathologies such as tissue degeneration, hypertrophy, hyperplasia, ruptured bile ducts amongst others. Findings suggest utmost caution on chronic use of the polyherbal mixture and avoidance whenever possible, as its hepatotoxic potentials are considerable.

Keywords: Herbal remedy; hepatotoxicity; hepatocytes; drug-induced liver damage; toxicity.

1. INTRODUCTION

In the Nigerian state, self-medication is a common practice. It often includes the co-administration of orthodox and herbal drugs and is not without dire consequences. The major functions of the liver include the detoxification and excretion of many endogenous and exogenous substances. Therefore, an injury to the liver or its functional impairment may complicate one's health and this constitutes one of the serious global public health challenges [1]. Due to its critical role in metabolism of xenobiotics, the liver's physiology may be compromised by repeated exposure to certain substances (including herbal remedies) be it intentionally or otherwise. Hepatotoxicity is often presented as distorted metabolic functions, glutathione depletion, lipid peroxidation and optimal cellular necrosis [1,2]. Additionally, biomarkers like alkaline phosphatase, alanine transaminase, aspartate transaminase, triglycerides, cholesterol and bilirubin are usually elevated in liver disease [2]. Drug-induced liver injury (DILI) is one of the many reasons why numerous drugs do not progress past preclinical testing and early phase clinical trials or are withdrawn from the market following post-market pharmacovigilance.

Dr Iguedo Goko Cleanser® is a polyherbal mixture licensed by National Agency for Food and Drug Administration and Control (NAFDAC) with registration number, A7-0804L. The product is popularly promoted among native Nigerians to be very effective against various disease conditions [3]. The product is made from the following medicinal plants: bitter leaf, garlic, ginger, sugarcane and pigeon pea [4]. The Nigerian state has witnessed use of herbal remedies to a manifold. This upsurge in patronage is due to the perceived efficacy and safety of herbal medicines, especially as they are promoted to end users as being 'natural and absolutely safe' and freely hawked due to little or no restriction and regulation of these products. These products are not devoid of both intrinsic and extrinsic factors that may provoke toxic health effects especially on chronic or intermittent exposures. This is believed to be so as several studies have associated herbal remedies to cases of poisoning [5-7]. Presently, there is dearth of information on toxicological assessment of various/popular herbal remedies sold across the oil-rich Niger-delta states of Nigeria both in animal and human studies. Therefore, this research was designed to determine the effect of repeated exposure to Dr Iguedo Goko Cleanser® on liver function parameters and liver histoarchitecture in exposed Wistar rats. It is thought that such findings will provide a rationale for the moderate use or avoidance of the product vis-à-vis 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 polyherbal mixture was purchased from a major distributor in Uyo metropolis, Nigeria, and the stock concentration as well as the administered doses was determined as earlier reported by Udom et al. [4].

2.2 Experimental Animals

The animals (Wistar albino rats of both genders; 120-160 g) 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 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 1.

The doses (30 and 10% of LD_{50}) were administered daily using oral gavage for 60 days of the test period [8,9]. 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 (ALT, AST, ALP, bilirubin, albumin and total plasma protein) investigations. The liver tissues were eviscerated for macroscopic and histopathological examinations.

2.3.1 Biochemical analysis

Serum transaminases: Aspartate transaminase (AST) and alanine aminotransferase (ALT) activities were determined at 340 nm according to the methods described by IFCC [10]. Alkaline phosphatase (ALP) was determined at 405 nm according to the method described by Tietz [11].

Total plasma protein was determined at 530 nm by measuring the presence of the basic amino acid residues, arginine, lysine and histidine, which contributes to formation of the protein-dye complex. The principle of this assay is that in an alkaline solution, copper ions react with protein peptide bonds to give a purple coloured biuret complex [10,11]. Also, serum albumin was assayed. Briefly, test tubes were labelled as blank, standard, control, samples and 1.5 mL of working reagent was dispensed into each tube, 0.01 mL (10 µL) of sample was added to respective tubes, mixed and allowed to stand at room temperature for 5 min. Serum albumin binds selectively to the dye bromocresol green at pH 4.2. The increase in absorbance of the resulting albumin-dye complex was read at 630 nm (wavelength range: 580 – 630 nm) and is proportional to the albumin concentration. The absorbance was taken and recorded.

Total and direct bilirubin was done using a colorimetric (DCA) method. Briefly, 100 µL (0.1 mL) of the sample was pipetted into a test tube and 1000 µL of the working reagent (prepared by mixing DCA reagent and nitrite reagent in a ratio of 50:1 by volume) was added, mixed thoroughly and incubated for 5 min at 37 ºC and read at 546 nm against the sample blank (prepared by adding 1000 µL of DCA reagent to 100 µL of the sample). Bilirubin reacts with 2, 4-dichloroanilline to yield azobilirubin, while the albumin-bound bilirubin is released by a detergent. The intensity of the colour produced is directly proportional to the amount of total bilirubin concentration present in the sample.

These biochemical investigations were done using automated analysers and Fortress Diagnostic Kits® according to standard procedures of manufacturer's protocols at Bridge Bio-Tech Ltd, Ilorin, Nigeria.

2.3.2 Histopathological examination

From each diethyl ether euthanized and sacrificed rats, the liver was immediately excised, freed from adventitia, blotted with tissue paper, weighed, sectioned and fixed in 10% buffered formalin for histological studies. The fixed sections were dehydrated with alcohol, cleared with xylene, infiltrated and mounted with paraffin wax, sectioned, rehydrated, stained with haematoxylin and eosin and mounted with coverslips for histopathological assays using light microscope at a magnification of 100. To minimize bias, the pathologist was denied knowledge of the doses and treatments given to the different groups of experimental rats [12].

2.3.3 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<0.05) were considered significant.

2.3.4 Limitations

Reversibility studies on the polyherbal mixture using the model described above was not carried out due to set limits [4].

Table 1. 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

3. RESULTS

3.1 Biochemical Analysis

Significant (p<0.05) reduction in the activity of ALT was recorded for low dose males (LDM) relative to control (CM) and high dose males (HDM). High dose females (HDF) had significantly elevated serum ALT activity compared to control females. Also, serum ALT activity was significantly reduced in low dose females relative to HDF. Though not statistically significant, an elevated ALT was also observed in the low dose females (LDF) relative to control. On an average, the female subjects had significantly low ALT activity compared to the males (Fig. 1).

Significant reduction in AST activity was recorded in experimental males relative to their control. Whereas serum AST activity was significantly reduced in high dose female rats, but elevated in low dose female rats relative to control female rats. High dose female rats had low serum AST activity relative to the males, while an elevation was recorded for the low dose females relative to the male rats. The activities of ALP were significantly reduced in the experimental male rats relative to their control. However, an elevation was recorded for the low dose males in comparison to the high dose males (Fig. 1). Significant increase in ALP activity was recorded for the female rats relative to their control. Nevertheless, serum ALP activity was significantly reduced in females compared to males.

There were no significant (p>0.05) differences in serum albumin levels across all test groups. There was no significant difference in the concentration of protein in the male rats. Compared to control females, high dose females and male rats, a significant reduction in protein was recorded for low dose female rats (Fig. 1). No significant differences were observed for direct bilirubin among the male rats. This was significantly reduced in low dose female rats compared to the control. Female rats had reduced direct bilirubin level compared to their male counterpart. High and low dose female rats had significantly reduced total bilirubin levels in comparison to the control females and the male rats respectively (Fig. 1).

3.2 Histopathological Assays

Histological examination of the liver of rats (both gender) in the control groups presented preserved/normal cellular architecture of the ductal cells, normal orientation of layers of blood vessels, well-spaced hepatocytes and presence of kupffer cells within the sinusoids. Whereas, those of the high and low dose experimental groups presented some forms of pathologies such as portal area with ruptured, degenerated and disoriented layers of bile ducts, hyperplasia of the ductal and connective tissue cells, abnormally spaced, hypertrophied and vacuolated hepatocytes, widened and disoriented sinusoids, tissue degeneration, ruptured bile duct and hyperplasia (Fig. 2).

4. DISCUSSION

In biological systems, aminotransferases are known to catalyze the conversion of amino acids and oxoacids. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are the two most clinically significant transaminases that catalyzes the redistribution of nitrogen between amino acids and oxoacids which are involved protein metabolism and gluconeogenesis [13]. Protein metabolism and gluconeogenesis, for the most part occurs in the liver. Thus, the transaminases (though not localized to the liver only) are predominantly found there. They are indeed ubiquitous in their cellular distribution. In an event of damage to tissues where they are localized, these enzymes are expected to be released into the bloodstream, causing markedelevations in their concentrations. Since

ALT and AST are predominantly found in the hepatic cytosol, it is generally accepted that their concentration in the serum must be markedly elevated following liver injury. However, since the transaminases are so ubiquitous in their cellular distribution, most serum elevations are associated with a variety of non-hepatic disorders. Thus, decrease in ALT or AST (normal enzymes found in the liver and kidney), may not always suggest a healthy liver or kidney. Rather, it may also suggest leakage into the surrounding tissues, and as such, is used as a 'marker' to ascertain early toxic effects of administered foreign compounds causing injury to the liver and kidney [14-16].

Abdelhalim and Moussa [17] ascribed increase or decrease of liver enzymes and kidney function parameters to a probable occurrence of liver and kidney injury. Since the liver contains high concentrations of ALT when working properly, liver damage causes the release of high concentrations of ALT into the bloodstream. However, the severity of liver damage does not necessarily correlate with the concentration of ALT in the blood. This is so, as the test measures only the amount of ALT in the bloodstream at a given point in time. Though many in the medical community as well as in medical publications commonly and incorrectly refer to the measurement of the aminotransferases as liver function test, it is important to clarify that due to the ubiquitous nature of the transaminases or lack of specificity particularly to the liver, they do not reflect the function of the liver, and as such, even in conditions when AST and ALT are markedly high, the liver may still function properly. Thus, they are tagged as 'nonspecific liver enzymes'. The precise levels of these enzymes do not necessarily correlate well with the extent of hepatic disorders and/or its prognosis. For instance, in acute viral hepatitis A, the patient's transaminases levels may be unusually high; however, most people diagnosed of this condition fully recover without cases of residual liver disease. On the other hand, patients diagnosed of chronic hepatitis C infection usually have a mere elevation in AST and ALT. However, the condition is associated with substantial liver injury as well as advanced scarring of the liver tissue from progressive minor inflammation to the liver. Therefore, the decreases and increases in the specific activities of ALT and AST recorded in the present study are suggestive of underlying physiopathological interplay in the organ of concern.

In contrast to the cytosolic enzymes ALT and AST, alkaline phosphatase (ALP) is a membrane bound enzyme that hydrolyses phosphate esters. In humans and other mammals, the ALP is found in the kidney, liver, bone, intestine, reticuloendothelial tissue and the placenta [18]. However, ALP activity in normal adult serum is majorly derived from the hepatic osseous and the reticuloendothelial tissues. Owing to its location in the hepatic sinusoid membrane, ALP is thought to be involved in cellular transport functions. Generally, sustained elevations in ALP serum activities are always associated with either liver or bone disorders or both. Therefore, these organs are of prime importance during differential diagnosis. Elevated ALP levels may be associated with an array of both primary and secondary liver conditions. For instance, cholestatic lesions secondary to intrahepatic or posthepatic disease conditions are marked with dramatic increases in ALP and gamma glutamyltransferase. Thus, serum ALP measurement is considered a sensitive biomarker or indicator for obstructive and space-occupying lesions to the liver [18]. In extensive biliary obstruction or diffuse liver cell disruption, bilirubin excretion is normally compromised; hence, the differential increase in ALP activity relative to serum bilirubin gives insight to the occurrence of obstructive or space-occupying liver conditions. According to Vroon and Israili [18], hepatic cell lesions are usually manifested by hyperbilirubinemia and dominant increases in serum transaminases, while ALP elevation may only be minimal. However, the findings of the present study revealed decrease and increases in serum ALP activities as well as decreases in total and direct bilirubin levels. Specifically, serum ALP activity was elevated in the low dose males, high dose and low dose female rats, while bilirubin levels were reduced in the female rats. In contrast to the report of Vroon and Israili [18], the variation in serum nonspecific liver enzyme vis-à-vis the bilirubin levels here recorded may be due to the fact that there were no lesions in the hepatocytes of the experimental animals as revealed by the histopathological assessment of the liver. The histopathological assessment of the liver presented some forms of pathologies such as portal area with ruptured, degenerated and disoriented layers of bile ducts, hyperplasia of the ductal and connective tissue cells, abnormally spaced and vacuolated hepatocytes, widened and disoriented sinusoids, tissue degeneration, ruptured bile duct and hyperplasia. This is in agreement with findings of Onyejike et

al. [19], who reported lobular inflammation, mild necrosis and some mild haemorrhage in all the test groups that were administered the herbal mixture. Physiologically, bile ducts are drainage pipes that carry bile from the liver to the gallbladder and from the gallbladder to the small intestine to aid the digestion of food. Ruptures in these drainpipes suggest that their transport function was compromised with an attendant effect on digestive processes. In this study, the histopathology report on the liver is indicative of a highly probable liver toxicity following exposure to the polyherbal mixture.

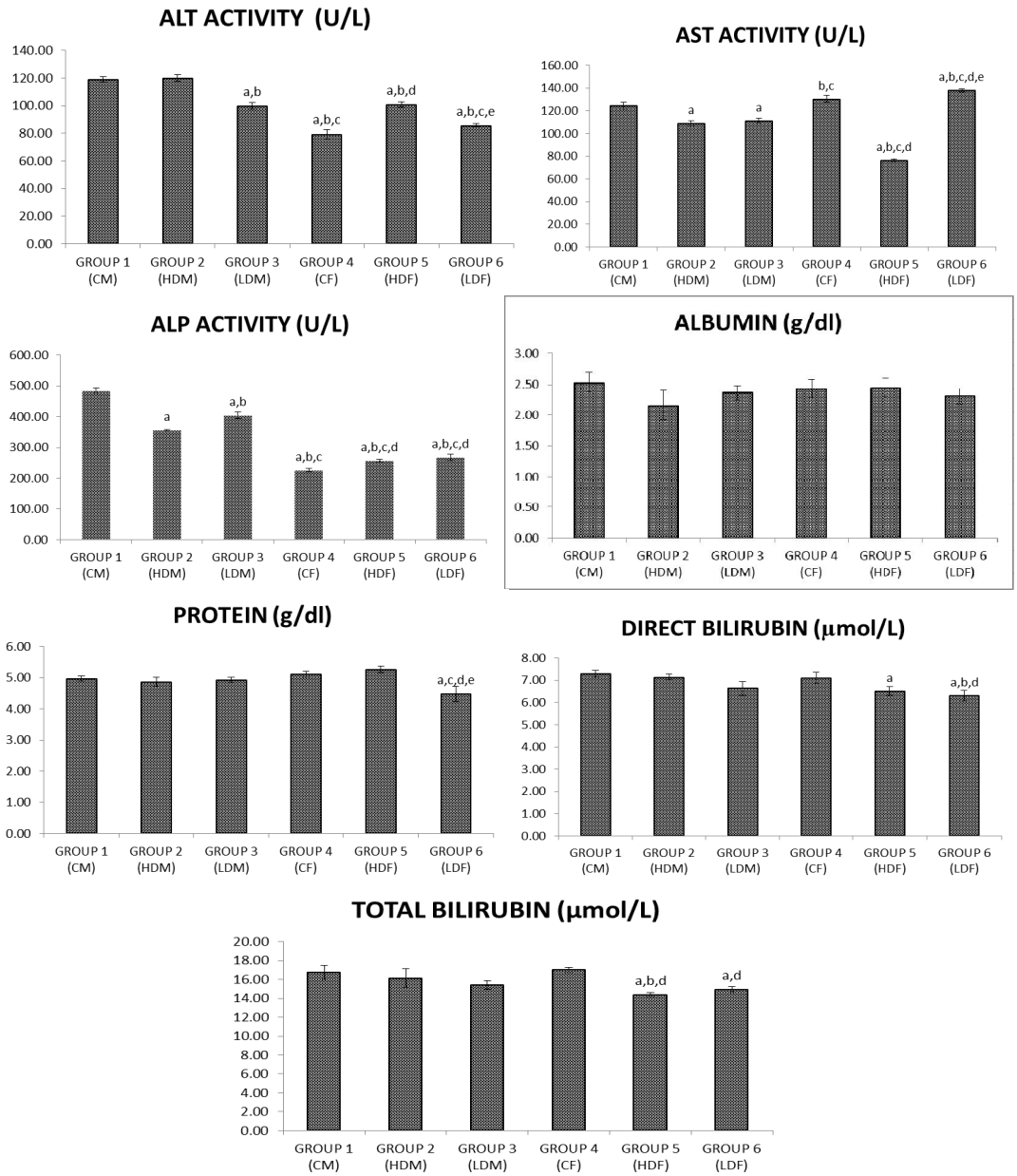

Fig. 1. Serum liver function parameters of Wistar rats exposed to Dr Iguedo Goko Cleanser®

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

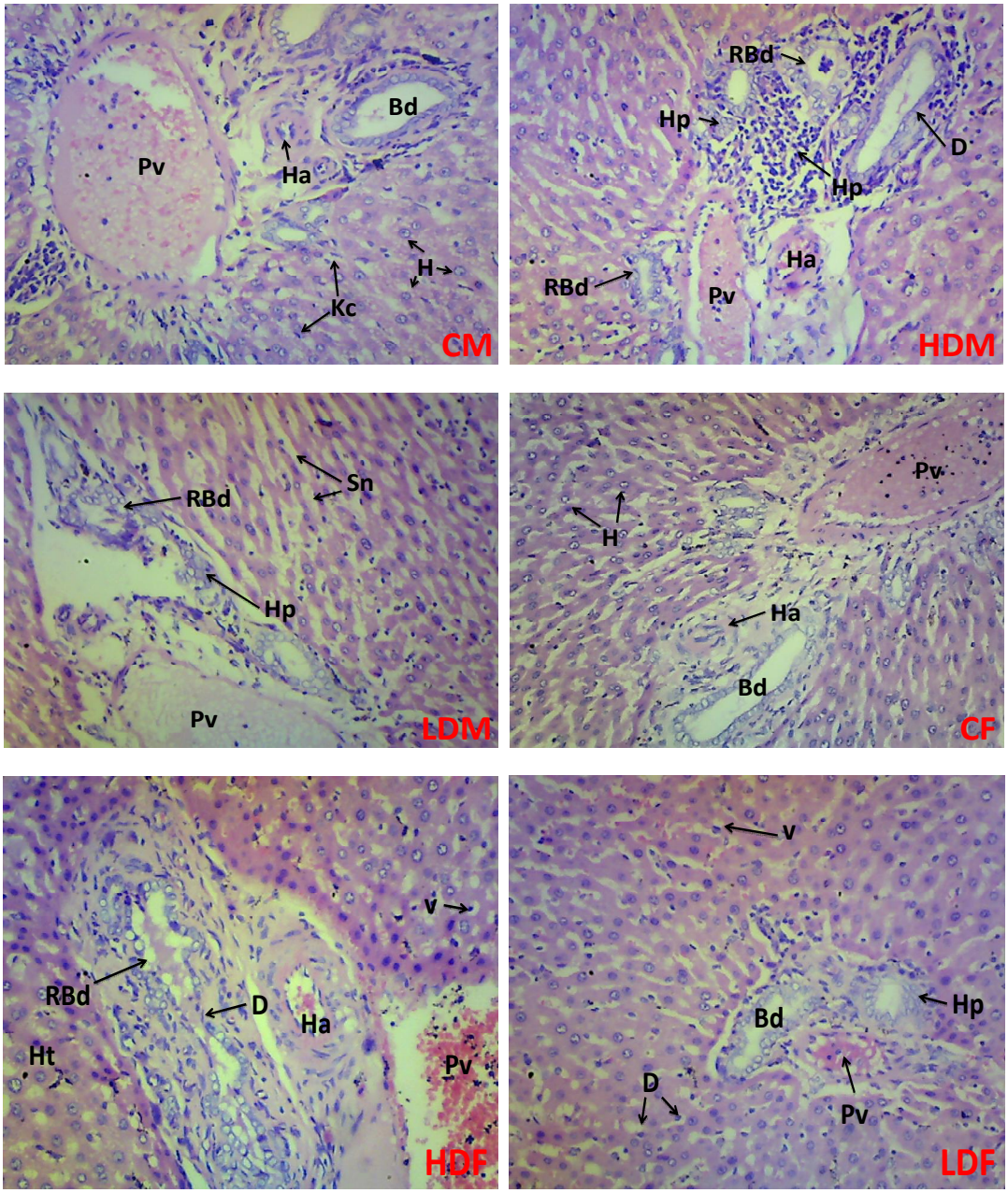

Fig. 2. Tyical liver sections from controls and Dr Iguedo Goko Cleanser® exposed Wistar rats

CM = Control males, HDM = High dose males, LDM = Low dose males, CF = Control females, HDF = High dose females, LDF = Low dose females, D = degeneration, Bd = bile duct, Sn = sinusoids, RBd = ruptured bile duct, Hp = hyperplasia, H = hepatocytes, Kc = kupffer cells, Pv = portal vein, Ha = hepatic artery, Ht = hypertrophy and v = hypertrophied and vacuolated hepatocytes x 100 magnification

5. CONCLUSION

Findings of this study highlight the inherent abilities of Dr Iguedo Goko Cleanser® to impair liver functions as well as disorient the cellular or histostructure of the hepatic cells. Contrary to the popular belief that herbal drugs are 100% natural, completely safe and devoid of any toxicity whatsoever; the present study point in the opposite direction. Therefore, the chronic (intermittent, continuous) or prolong use of Dr Iguedo Goko Cleanser® should be done with

utmost caution, and wherever possible, be avoided.

DISCLAIMER

It should be noted that the products employed in this research are common products in our area of research and country. There is absolutely no conflict of interest whatsoever between the authors and manufacturer of the products especially as the authors do not intend to use these products as an avenue for any litigation but for the advancement of scientific knowledge. Also, the research received no funding from any external body (the manufacturers of the test substance inclusive) rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

This study was ethically approved by the Experimental Ethics Committee on Animal Use of the Faculty of Pharmacy, University of Uyo, Nigeria and was conducted in accordance with the National Institute of Health Guide for the Use of Laboratory Animals (NIH, 1996).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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