

**TOXICITY STUDIES OF YOYO CLEANSER BITTERS POLY-
HERBAL FORMULATION IN ALBINO RATS****Timipa R. Ogoun¹, Odangowei I. Ogidi*² and Thomas Aye²**

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ABSTRACT

There is a resurgence of interest in the use of herbal supplements in developing countries arising from the unsubstantiated belief of the safety of the supplements. The toxicity of a popular Nigerian poly-herbal preparation (Yoyo cleanser bitters) on biochemical functions of the liver and kidney of albino rats was investigated. Twenty (20) adult albino rats were used for this research. Yoyo cleanser bitters treated groups (n=5) was administered to each rat at 5, 10 and 15 mg/kg body weight. Treatment of the animals was done for 14 days after the 7 days acclimatization before sacrificing them through cervical dislocation. Blood was collected by cardiac puncture, using 5ml syringes and 23G needles into blood sample containers for biochemical analysis using

the standard principles of biochemical analysis. The result of the study shows minimal and non- significant increase of alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST), albumin, creatinine, total bilirubin and total protein of the herbal formulation when compared with the control. However, there was a significant increase in serum levels of urea (10 and 15 mg/kg doses) and total cholesterol (TC) (5 and 10 mg/kg doses) on the treated groups. It can therefore be concluded that the poly-herbal formulation at the used doses and duration of the study on AST, ALP, ALP, albumin, creatinine, total bilirubin and protein might not cause any form of cholestasis and may not impair the capacity of the liver to excrete bilirubin. They might not also have a reno-toxic effect on the kidneys due to the reduced levels of creatinine. But on some increased values of urea and TC which might lead to reduced renal function and hepatobiliary disorder and

impaired cholesterol metabolism and as such a call for caution on the use of the poly-herbal formulation on higher therapeutic doses and longer duration of time.

KEYWORDS: Yoyo cleanser bitters; Toxicity; Liver; Kidney; Biochemical parameter; Albino rats.

1. INTRODUCTION

The World Health Organization (WHO) has defined herbal medicine as: ‘any part of the plant in which one or more of its parts can be used for therapeutic purposes or as precursors for the synthesis of useful drugs’.^[1] Herbal remedies have been used for several years by people from diverse cultures. Prior to the advent of modern medicine, the use of herbal medicine was the only available treatment known to mankind. During the past decades, the general population globally has developed an unparalleled interest in self-medication with natural therapies especially herbal medicine.^[2,3]

These herbal supplements are taken routinely without medical consultation or disclosure. There are bold and popular perceptions that, because the products are natural, they are safe and that they have been used for centuries without harmful effects. Other reasons are – its accessibility and availability at minimal cost. The long history of use for herbal supplements is not a guarantee of safety, particularly with long-term use, at high doses, or with comedications and/or co-morbidities.^[4] Based on the reports of WHO, the use of herbal medicine throughout the world has exceeded the use of conventional therapies by two to three times.^[5]

Yoyo bitters is one of the most popular of these bitters. Yoyo cleanser Bitters is an herbal oral preparation popularly used in many parts of Nigeria. It is one among the class of bitters produced by Abllat Nigeria Company Limited, an indigenous health care product provider. It is a botanic medicine launched into the Nigerian market in the year 2003. Since its introduction into the Nigerian drug market, it has received wide acceptance and use by the general populace.^[6] The drug is registered and certified by National Agency for Food and Drug Administration and Control (NAFDAC) as the first real bitters without alcohol, colouring or artificial preservatives produced in Nigeria.

The Yoyo cleanser bitters are composed of five herbal constituents, they includes *Aloe vera* (True aloe, Lily of the forest), *Acinos Arvensis* (Basil thyme), *Citrus aurantifolia* (Bitter

orange), *Chenopodium murale* (Nettleleaf goosefoot) and *Cinamomum aromaticum* (Cassia). It also contains water soluble vitamins and minerals e.g. Vitamins (B1, B2, B3, B6, and B12), Mineral (copper, zinc, iron) added to fortify the herbal preparation.^[7]

Its usage has been popularly attached to its claimed effect on the management of ailments of the digestive System: (1) It decreases the stomach acidity in cases of ulcer, (2) It diminishes the irregular production of gastric juice, (3) It stimulate the liver to ensure proper and complete digestion and (4) It helps to digest heavy and fatty foods. In the Circulatory System: (1) It enhance blood circulation, (2) Helps to facilitate reduction in blood pressure through arteries dilation and (3) Assists in the elimination of cholesterol, sugar, triglycerides, creatinine and uric acid. In Nervous System: (1) It enhances effective function of the secretive glands and (2) It is beneficial in the treatment of such disorders as insomnia, stress and depression. In the Urinary and Excretory Systems: (1) It facilitates the process of blood purification by the kidneys, (2) It help to dissolve existing kidney stones and to prevent the formation of new ones, (3) It prevents kidney and bladder infections and (4) It helps to normalize the operation of the intestine for excretion of faeces. In ulcerations: (1) It inhibits ulceration by eliminating any traces of stored toxins in the body system and (2) Aid boosting body immunity. In Hardening of Tissues: (1) It dissolves any encased toxic materials in the body and (2) Enhances cell formation and growth. In cases of Over Weight: (1) It reduces excess body fat and (2) Encourages healthy weight loss.^[8]

Despite these widely documented medicinal uses of this formulation, there exists a paucity of experimental data on the likely toxic effect of the herbal drink especially as it relates to vital organs of the body such as the liver and kidney. The aim of this research was to evaluate the toxicity effects of Yoyo cleanser bitters by assessing the biochemical liver and kidney functional indices occasioned by the consumption of the herbal formulation using albino rats as the animal models.

2. MATERIALS AND METHODS

2.1. Materials and chemicals

Syringes and needles, hand Gloves, incubator, glucometer, Aucku check active strip micropipette, stop watch, oven, centrifuge Model 800, cotton wool, HPLC, and GCMS. The chemicals included 10% Chloroform, xylene, hemotoxylin and eosin stains.

2.2. Collection of herbal formulation samples

Yoyo Cleanser Bitters a Nigerian Herbal formulation was purchased from a registered pharmaceutical shop (Cynflac Pharmacy Yenagoa, Bayelsa State). The product is a combination of several medicinal plants. As an inclusion criterion, the product was ascertained to have been registered with the National Agency for Food, Drug Administration and Control (NAFDAC number: A7-1051L). The manufactured and expiry dates of the product were inspected and all were confirmed to be within the acceptable time frame. The Manufacturer's seal, inspected to ascertain the authenticity of the product was intact in the bottles of the syrup purchased for the analysis and was taken to the Research Laboratory, Department of Pharmacology, Faculty of Basic Medical Sciences, College of Health Sciences, Niger Delta University, Wilberforce Island, Bayelsa State and was stored under room temperature prior to the experiment.

2.3. Experimental animals

2.3.1. Animal handling

Twenty (20) adult albino rats used for this study were purchased from the animal house of the Faculty of Basic Medical Sciences, College of Health Sciences, Niger Delta University, Wilberforce Island, Bayelsa State. The animals were kept in standard plastic rat cages in the research laboratory of the Department of Pharmacology, Faculty of Basic Medical Sciences, College of Health Sciences, Niger Delta University, Wilberforce Island, Bayelsa State. The animals were allowed to acclimatize for 7 days under standard laboratory conditions with free access to commercial grower's mash (Delta Feeds), water *ad libitum* and 12 h/ 12 h light/darkness cycle and fresh air prior to the inception of this study. The animal experiment was conducted in accordance with internationally accepted practice for laboratory animals and approved by the Animal Ethics Committee of the Faculty of Basic Medical Sciences, College of Health Sciences, Niger Delta University, Wilberforce Island, Bayelsa State.

2.4. Administration of poly-herbal formulation

The herbal formulation was administered using 5 ml syringe, the corresponding dose was given to each rat based at 5, 10 and 15 mg/kg body weight dose of the herbal formulation was selected.

2.5. Experimental Design

After the period of acclimatization, the animals were randomly divided into experimental and control groups. The albino rats were grouped and herbal formulation administered as follows;

Group 1 (n = 5) Control: Albino rats received 2ml of distilled water daily within the period of the study before sacrificing.

Group 2 (n = 5) Albino rats were treated with 5 mg/kg body weight of Yoyo Cleanser Bitters.

Group 3 (n = 5) Albino rats were treated with 10 mg/kg body weight of Yoyo Cleanser Bitters.

Group 4 (n = 5) Albino rats were treated with 15 mg/kg body weight of Yoyo Cleanser Bitters.

2.6. Blood sample collection

The animals were observed in their cages for clinical symptoms daily and at the end of the 14 days treatment, the rats were sacrificed under chloroform anesthesia and blood was collected by cardiac puncture, using 5ml syringes and 23G needles into blood sample containers. The blood was allowed to stand for 2 hours to coagulate and was centrifuged for 10 minutes at 2000 rpm and the supernatant (Serum) carefully collected for biochemical analysis.

2.7. Biochemical analysis

Serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were determined following the principle described by Reitman and Frankel^[9] while the alkaline phosphates (ALP) were carried out according to the method described by Roy^[10] to assess liver function. Renal function was assessed by measuring plasma creatinine (CREA) levels and blood urea nitrogen (BUN) was assayed following the method of Fossati et al.^[11] and Skeggs.^[12]

In order to assess the synthetic function of the liver, total serum protein (TP), Total bilirubin and albumin (ALB) concentrations were determined according to the principles based on the Biuret reaction^[13] and bromocresol green reaction^[14] respectively. Total Serum cholesterol (TC) concentrations were estimated following the method described by Trinder.^[15]

2.8. Statistical analysis of data

All data were expressed as mean \pm standard error of mean (SEM). Significant differences among the groups were determined by one-way analysis of variance (ANOVA) using the statistical analysis program for social sciences (SPSS 17.0).

3. RESULTS

3.1. Biochemical parameters

Table 1 shows the Body Weight of Animal with the herbal formulation. Table 2 shows the effects of Yoyo Cleanser Bitters herbal formulation on Biochemical Parameters of wistar albino rats in 5, 10 and 15 mg/kg body weight. The biochemical parameters analyzed were ALP, AST, ALT, total bilirubin, total protein, albumin, creatinine, urea and total cholesterol levels in the experimental animals and were compared with the control. The mean values of some of ALT, albumin and creatinine analyzed were significantly lower while some of the dosages of AST, ALP, total bilirubin, urea, total cholesterol were higher in the experimental animals as compared to the controls. There was a significant difference of total protein at ($P < 0.05$).

Table 1: Body Weight of Animal with the herbal formulation.

Control	Yoyo Cleanser Bitters		
	5mg/kg	10mg/kg	15mg/kg
98±0.9	121±1.8	147±1.45	117±1.4

(Mean ± SEM, n = 5)

Table 2: Effects of Yoyo Cleanser Bitters herbal formulation on Biochemical Parameters of albino rats.

Biochemical parameters	Control	Yoyo Cleanser Bitters		
		5mg/kg	10mg/kg	15mg/kg
Total Bilirubin (mg/dl)	0.37±0.02 ^a	0.42±0.03 ^a	0.43±0.03 ^a	0.33±0.02 ^a
Total Protein (g/dl)	4.8±0.12 ^b	4.8±0.11 ^a	5.5±0.18 ^d	6.1±0.44 ^c
Albumin (g/dl)	5.2±0.15 ^a	4.2±0.12 ^a	3.7±0.18 ^a	4.2±0.31 ^a
Creatinine (mg/dl)	0.58±0.01 ^b	0.47±0.02 ^b	0.55±0.02 ^b	0.43±0.02 ^b
Alkaline phosphatase, ALP (u/l)	70.4±0.14 ^b	68.6±0.08 ^b	76.2±0.17 ^b	74.5±0.20 ^b
Aspartate aminotransferase, AST (u/l)	50.4±0.15 ^d	71.3±0.24 ^d	64.4±0.15 ^d	54.3±0.30 ^d
Alanine aminotransferase, ALT (u/l)	32.1±0.12 ^d	26.5±0.17 ^d	28.7±0.17 ^d	26.7±0.17 ^d
Urea (mg/dl)	16.8±0.05 ^c	16.7±0.18 ^c	18.6±0.17 ^c	20.1±0.18 ^c
Total Cholesterol (mg/dl)	67.5±0.26 ^c	70.7±0.65 ^c	81.3±0.17 ^c	62.4±0.23 ^c

Values are presented as means ± SEM; n=5. Values bearing different superscript alphabets are significantly different ($p < 0.05$)

4. DISCUSSION

The implementation of the need to increase public awareness and education for healthcare professionals and the general populace about the potential dangers of herbal preparations, in addition to the regulation of their proliferation by the various Food and Drug Administrations cannot be overemphasized.^[16-18] In spite of the high consumption of herbal products or

remedies among the Nigerian population and in most developing countries, much attention has not been given to the evaluation of the safety of these preparations.

‘Marker enzymes’ are biochemical parameters associated with health indices, which are always of diagnostic significance in the routine clinical evaluation of the state of health. In this present study the safety of yoyo cleanser bitters, a Nigerian poly-herbal formulation was evaluated by assessing their effects on markers of renal, hepatic and kidney functions on wistar albino rats.

The result obtained in the alkaline phosphatase (ALP) activity recorded in 5 mg/kg body weight of Yoyo Cleanser bitters (Table 2) was lower than the control. Reductions in the ALP activity in the liver have been reported to be as a result of a compromised in the functionalities of the hepatocytes, bile ducts or gall bladder system.^[19] The reductions in the ALP activity in the tissues could have led to the inadequate transportation of needed ions or molecules across their cell membranes and the inhibition of metabolic processes, such as the synthesis of nuclear proteins, and nucleic acids. However, at 10 and 15 ml/kg dosage of Yoyo bitters, there was a slight increase in ALP values when compared to the control. The result is in accord with the works of Omotosho et al.^[20]

The increase obtained in the ALP activity might indicate that the administration of Yoyo bitters increased the functional activity of ALP that probably led to *de novo* synthesis of the enzyme molecules *in situ*. It is imperative to note that this hyper-activity of ALP could lead to a threat to the survival status of the cells dependent on a variety of phosphate esters, as indiscriminate hydrolysis of phosphate esters in the tissues could result in cytolysis, autolysis and consequently hemolysis. This result is synonyms with the finds of Martins et al.^[21]

From the results of this study AST concentrations obtained in 5, 10 and 15 mg/kg were observed to be higher than the control. Since AST is not specific for liver function, the increase in its activity in the herbal formulation may reflect hepatic and/or extra-hepatic toxicity. The mild to moderate increase in plasma aminotransferases observed in this study was not associated with a decline in the metabolic function of the liver which is in consonance with the findings of Martins et al.^[21]

The reduction and very slight increase in the ALP and total bilirubin levels in the polyherbal formulation compared to that of the control of this study is an indicative that Yoyo bitters did

not cause any form of cholestasis and did not impair the capacity of the liver to excrete bilirubin. Liver disease is characterized by an elevation in the plasma level of alkaline phosphatase (ALP), while hyperbilirubinaemia is seen in conditions causing hepatic liver diseases that impair the excretion of bilirubin.^[22]

The significant decrease in serum levels of albumin observed in this study may also be indicative of liver impairment. Serum albumin is quantitatively the most important protein synthesized by the hepatocytes and reflects the extent of functioning liver cell mass. Therefore, decreased serum levels of albumin occur when there is impairment in the synthesizing function of the liver.^[23] The reduction of serum albumin and minimal increase of serum total protein in 10 and 15 mg/kg of the herbal formulation treated groups compared to that of the control of this study is an indication that Yoyo bitters may not cause any dysfunction in the synthetic function of the liver.^[22] The finding in this study is in agreement with the works of Bukoye and Bamidele^[24] and Anionye et al.^[25]

The reduced levels of creatinine probably indicate that the bitters did not interfere with the renal capacity to excrete these metabolites. The lack of significant difference between the metabolites of the control and bitters treated groups used in assessing the kidney function status may also be a reflection of the preserved renal integrity of the treated rats.^[26] Hence the bitters can be said not to have a reno-toxic effect on the kidneys of the bitters fed rats as they preserved its renal integrity and did not affect its capacity to excrete metabolites. However, the significant increase in serum levels of urea at 10 and 15 mg/kg dosage observed in the treated groups may be due to nephrotoxic effect of the herbal formulation, leading to reduced renal function. Urea levels are used as markers of kidney function, though the test for creatinine is more sensitive than urea.^[23]

Thus, elevated serum levels of urea may indicate kidney injury, with resultant reduced glomerular filtration. Urea is formed in the liver, representing the principal waste product of protein catabolism and is excreted by the kidney. The poly herbal formulation probably causes a decrease in glomerular filtration rate, resulting in decreased excretion of urea, which may produce an increase in the concentration of the blood urea.^[27]

The minimal increase in 5 and 10 mg/kg observed in serum total cholesterol in the treated groups may be due to the effect of the herbal formulation. Cholesterol may increase due to hepato-biliary disease. The increase in the serum levels of total cholesterol may be attributed

to the toxic effect of the formulation, leading to hepatobiliary disorders and impaired cholesterol metabolism. These findings are in agreement with Omotosho *et al*^[20] and Odangowei *et al*.^[28]

5. CONCLUSION

The result of the present study has shown that the minimal and non- significant increase of ALP, AST and ALT, albumin, creatinine total bilirubin and total protein (5, 10 and 15 mg/kg dosages) of Yoyo Cleanser Bitters when compared with the control had no toxic effect. It can therefore be concluded that the poly-herbal formulation at these doses and duration of study might not cause any form of cholestasis, and may not impair the capacity of the liver to excrete bilirubin. They might not also have a reno-toxic effect on the kidneys due to the reduced levels of creatinine recorded. However, the significant increase in serum levels of urea (10 and 15 mg/kg dosages) and total cholesterol (5 and 10 mg/kg dosages) observed in the treated groups may be due to nephrotoxic and hepato-biliary effects of the herbal formulation which might lead to reduced renal function and hepatobiliary disorder and impaired cholesterol metabolism.

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CONFLICT OF INTEREST

All authors declare that there is no conflict of interest in this work.

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