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Evaluation of the Potential Toxicity of the Starch from the Shoot of *Borassus Aethiopum* Mart in Wistar Rats

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: The shoot of *Borassus aethiopum* is cultivated and consumed in Northern Nigeria. Its starch has been investigated for use in pharmaceutical formulation but have limited studies on its toxicity. Toxicity is the degree to which a substance (a toxin or poison) can harm humans or animals. The plant *Borassus aethiopum* Mart belongs to the family Aracaceae, commonly known as the African Fan Palm. The shoot of the plant is commonly referred to as "Muruchi" in Hausa and is widely available and edible.

Objective: This experimental research was designed to examine the potential toxicity of the starch from the shoot of *Borassus aethiopum* in acute and subacute studies using Wistar rats.

Material and Methods: Fresh shoots of *Borassus aethiopum* were obtained, washed, peeled and grinded using mechanical grinder. The starch was extracted using water. Acute toxicity was carried out using OECD guideline 425. Healthy rats of both sexes were randomly grouped into four groups of six rats each (n=6) for the 28-days oral toxicity study. Distilled water was administered at the dose of 2ml/kg to group I which served as the control while groups II, III and IV were orally administered the starch from the shoot of *Borassus aethiopum* at the doses of 300, 600 and 1200 mg/kg daily for 28 days respectively. The animals were sacrificed after 28-days at which the blood samples were collected through cardiac puncture into plain and EDTA-containing tubes for biochemical and haematological analyses respectively. The liver, kidney, heart and spleen were excised, weighed and examined macroscopically.

Results: The phytochemical screening reveals the presence of alkaloids, tannins, and carbohydrate. The acute toxicity (LD_{50}) of *Borassus aethiopum* was found to be greater than 4000 mg/kg body weight. No notable and significant changes in the relative organ weight as well as the levels of the renal and hematological biomarkers when compared with the control. However, there was significant increase in serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT).

Conclusion: In conclusion, the results of this study indicated that the starch from the shoot of *Borassus aethiopum* showed some evidence of potential toxicity on the liver but did not affect the renal and haematological parameters.

Keywords: Acute; Sub-acute; Starch; *Borassus aethiopum*; Toxicity

INTRODUCTION

Toxicity is the study of the relative ability of substance to cause harmful effects on living organisms which can be at the cellular (cytotoxicity) or the organ (organ toxicity) level (Denny and Stewart 2013). Many of the plants used as food or medicine contain bioactive constituents which may be beneficial or harmful (potentially toxic) to man. However, studies revealed that many of the well-known plants found to be useful in traditional medicine are not harmless (Fennell *et al.,* 2004; Merlin *et al.,* 2019). Therefore, this necessitate the importance to investigate the toxic effects of medicinal plants that are increasingly used in local health practices. Medicinal Plants have long been used for curing diverse ailments in different traditional systems of medicine from antiquity and a substantial number have shown to be effective in the treatment of these medical ailments (Rajasekar *et al*., 2010). Toxicity has been reported in laboratory animal's studies which appeals for concern in situation of chronic use. Medicinal plants contain a wide variety of biologically active constituents which have been sources of many conventional drugs in use today and still serve as lead compounds for potentials development as drugs (Newman, 2008). The biologically active constituents also called secondary metabolites exhibit broad actions on the physiological system (Mussie *et al.,* 2015).

These secondary metabolites play important roles of defense in plants for survival (Tasneef ,*et al*., 2013) and in human body produce pharmacological actions that are beneficial to the health of individuals. Sometimes these actions elicited could be harmful to the living cells with ultimate damage (Nasir, 2013). Therefore, despite the historical use of medicinal plants, many of them lack adequate scientific evidence on their safety, effectiveness and mechanism of actions. The plant *Borassus aethiopum* Mart (family Arecaceae) has been described as a palm tree with huge fan shaped leaves. The young germinating shoot of the plant is called "Muruchi" in Hausa language. The fruits and shoot are consumed as food. Similarly, the shoot is consumed for aphrodisiac effect (Adamu, *et al.,* 2015). The flower is used against aphonia while the young leaves to stop haemorrhage (Orwa *et al.,* 2009). The potentials of *Borassus aethiopum* as pharmaceutical raw material merits explorations of its toxicity which has not been adequately studied. It will be helpful to expand the database on the toxicity of the starch of *Borassus aethiopum*.

Therefore, safety evaluation of medicinal plants requires that biomarkers which indicate a pathological process and/or disease conditions by increase or decrease of the variables as a suggestion of damage or impairment of an organ be assessed. Biochemical parameters and histopathological examination are often used in toxicity studies of medicinal plants and drugs on liver, kidney, heart, and other organs of metabolism and excretion in the body.

METHODOLOGY

Collection and identification of plant materials

The fresh shoots of *Borassus aethiopum* were collected from Hong Local Government Area of Adamawa State Northeast Nigeria in November, 2018. The plant material was identified by a plant Taxonomist in the Department of Biological Science and subsequently deposited in Pharmacognosy herbarium with the voucher specimen number UM/FPH/019/001/003, University of Maiduguri, Borno State.

Preparation and extraction of starch from fresh *Borassus aethiopum* shoots

The method used in the extraction of starch from *Borassus aethiopum* shoot by Muazu *et al* (2014) was adopted. Foreign materials were removed from the shoots and two (2) kilograms of fresh *Borassus aethiopum* shoots was washed and peeled using a stainless steel knife. The fibers on the

shoots were removed. The peeled shoots were washed with distilled water two times and allowed for some time for the water to drain. The *Borassus aethiopum* shoots were reduced to small sizes and pulverized using mechanical grinder. The pulp was soaked in enough quantity of water which was then passed through a sieve of 180µm diameter and allowed to stand for three hours. After sedimentation, the filtrate was decanted while the sediment (starch) was treated with 0.1N Sodium hydroxide in order to separate the starch and proteinous materials. The starch was washed several times with distilled water at an interval of an hour to allow the starch to sediment and decant the filtrate to remove excess sodium hydroxide. This was followed by gently decanting the water and centrifuging the suspension at 4000 rpm for five minutes. The *Borassus aethiopum* starch extracted was air dried at room temperature and size reduced using porcelain mortar, weighed and stored in an air tight container for further use.

Animal experiments

Twenty-eight (28) healthy Wistar rats of both sexes weighing (120-190g) were used in this study. The rats were obtained from the animal house of Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Maiduguri and were checked for signs of illness and anomalies. Animals were housed under

controlled environmental condition at room temperature and allowed to acclimatize for a period of seven days to the laboratory environment before being used for the study. They were fed with standard diet *ad libitum* and allowed free access to water. The weights of the Animals were determined using a weighing balance and randomized into different groups for the study.

Phytochemical screening

The starch from the shoot of *Borassus aethiopum* was used for phytochemical screening using the standard methods of Evans, 2002 and Sofowora, 1993 as adopted by Mohammad (2014). A small portion (0.5-1g) of the dry extract was subjected to the phytochemical tests to identify the presence of the phytochemical constituents.

Toxicity Study

Acute toxicity study

The acute toxicity study was performed based on the modified method described by the Organization for Economic Cooperation and Development (OECD) guideline 425 for testing of chemicals (OECD, 2008). Two groups with two healthy rats each were weighed to determine the weight and fasted overnight before the administration of the starch from the shoot of *B. aethopium*. The animals in group I were orally administered 2000 mg/kg body weight of the starch from the shoot of *B. aethiopum* and closely monitored for 48 hours for any sign of toxicity including mortality. Subsequently, after 48 hours, animals in group II were orally administered 4000 mg/kg body weight of the starch and observed for 48 hours. The animals in both groups were further observed daily for ten days for mortality and any sign of toxicity.

Sub-acute toxicity study

Subacute toxicity study was performed according to the Organization of Economic Cooperation and Development (OECD) guideline 407 for testing of chemicals which is repeated dose 28-days oral toxicity study in rodents (OECD, 2008). Animals of both sexes were randomly grouped into four groups of six rats each (n=6). Group I received distilled water 2ml/kg which served as the control while groups II, III and IV were orally administered the starch from the shoot of *Borassus aethiopum* at the doses of 300, 600 and 1200mg respectively daily for 28 days.

The animals were observed for signs of toxicity and mortality. The body weights were measured weekly for the period of 28 days, the food and water intake were monitored. At the end of the study, all animals survived and were anesthetized with ketamine and sacrificed. Blood samples were collected via cardiac puncture into EDTA and plain bottles for hematological (haemoglobin, hematocrit, red blood cells and white blood cells counts) and biochemical (alkaline phosphatase (ALP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT), chloride (Cl^-), potassium (K^+), sodium (Na^+), urea and creatinine) analysis respectively. After blood collection from the rats through cardiac puncture, the internal organs (liver, kidneys, spleen, and heart) were harvested, observed macroscopically for any gross lesions and weighed on a Mettler weighing balance to determine organ weights (Das et al., 2015). The body and organ weights of the rats was used to calculate relative organ weight ratio using the formula;

Relative organ weight ratio = organ weight / body weight x 100.

Statistical Analysis of Data

Data were analyzed for statistical significance using one-way analysis of variance (ANOVA). The results were expressed as Mean ± Standard Error of the Mean (SEM) in tables. Statistical package for Social Sciences (SPSS) version 20 software was used for the analysis. Results were considered significant at a P value of <0.05.

RESULTS

Qualitative phytochemical constituents of the starch from the shoot **of *Borassus aethiopum***

The preliminary phytochemical screening of the starch from the shoot of *Borassus aethiopum* was found to contain alkaloids, tannins and carbohydrates but no presence of saponins and triterpenoids (Table 1).

Table 1: Preliminary phytochemical constituents of the starch from the shoot of *B. aethiopum*

Phytochemical constituents	Result
Saponins	-
Alkaloids	+
Tannins	+
Triterpenoids	-
Carbohydrates	
Combined reducing sugars	+
Ketosis (Salivanoff) test	+
Molish's test	+

Determination of the acute toxicity of the starch from the shoot **of *Borassus aethiopum***

Oral administration of the starch from the shoot of *Borassus aethiopum* at the initial dose of 2000 mg/kg and at the dose of 4000 mg/kg administered 48 hours after the initial dose did not cause any mortality neither sign of toxicity on acute exposure or during the 10 days of observation. No significant weight loss was observed. Therefore, the LD_{50} (acute toxicity) of the starch from the shoot of *Borassus aethiopum* after oral administraion was found to be greater than 4000 mg/kg (Table 2). There were no observable changes in the gross behaviour of the animals. The rats were alert and responded to physical stimuli during the study

Table 2: Oral acute toxicity study of the starch from the shoot of *Borassus aethiopum* in Wistar rats

Groups	Animals per group	Dose (mg/kg)	Death Recorded
I	2	2000	No death
II	2	4000	No death

LD50>4000 mg/kg

Effect on renal function biomarkers of the starch from the shoot of *Borassus aethiopum* on rat in sub-acute toxicity

The parameters of the renal function showed no significant decrease in the concentrations of the electrolytes (sodium, potassium, chloride), urea and creatinine after 28 days of oral administration of the starch in the treated groups as compared to the normal control except for creatinine at the dose of 1200 mg/kg which was significantly decreased (Table 3).

Table 3: Effect of starch from the shoot of *B. aethiopum* on renal parameters in the sub-acute toxicity

	Mean±SEM			
Parameter(mMol/L)	**Control**	**300 mg/kg**	**600 mg/kg**	**1200 mg/kg**
Na^+	147.00±3.58	147.00±1.08	141.25±1.44	143.25±1.31
K^+	7.60±1.11	5.63±0.29	5.45±0.10	5.87±0.22
Cl^-	107.25±1.03	104.50±1.32	103.75±0.85	107.00±0.68
Urea	7.10±0.69	6.38±0.34	5.98±0.27	5.65±0.96
Creatinine	91.75±14.61	94.00±10.42	83.00±9.28	58.75±3.01*

Values were expressed as Mean ± Standard Error Mean (SEM), (n=6); one-way ANOVA. Na+, K+, and Cl-, represent sodium, potassium, and chloride concentrations respectively, urea and creatinine concentrations. Parameters were measured in (mMoL/L). Values marked with * were significantly different at $p<0.05$ compared with control

Effect on serum liver enzymes of the starch from the shoot of *Borassus aethiopum* on rat in sub-acute toxicity

The concentration of the serum liver enzymes marker aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were significantly increased at the dose of 300 mg/kg in the treated group as compared to the normal control (NC) after oral administration of the crude shoot extract of *B. aethiopum* for 28 days while the AST and ALT levels at the doses of 600 and 1200 mg/kg were near normal. On the contrary, the serum alanine phosphatase (ALP) was significantly decreased at the dose of 600 mg/kg after oral administration of *B. aethiopum* when compared with the normal control (Table 4).

Table 4: Effect of starch from the shoot of *B. aethiopum* on rat serum liver enzymes in the sub-acute toxicity

	Mean±SEM			
Parameter(U/L)	**Control**	**300 mg/kg**	**600 mg/kg**	**1200 mg/kg**
ALP	179.75±9.08	184.75±8.05	149.00±6.10*	159.75±9.84
AST	63.25±3.75	119.00±12.12*	88.00±7.65	75.75±7.32
ALT	30.75±1.18	40.50±3.12*	34.00±1.78	32.00±0.41

Values were expressed as mean ± SEM (SEM= Standard Error Mean), (n=6); one-way ANOVA. ALP, AST and ALT represent serum alkaline phosphatase, aspartate aminotransferase, and Alkaline aminotransferase respectively. Values marked with * were significantly different at $p<0.05$ compared with control.

Effect of the starch of *Borassus aethiopum* on hematological parameters of the rats in the sub-acute toxicity

The result of this study did not indicate significant difference in the levels of the white blood cells (WBC) count, red blood cells (RBC) count, hemoglobin and hematocrit concentrations in the treated groups as compared to the normal control ($P>0.05$) after 28 days of oral administration of the extract of *B. aethiopum* (Table 5).

Table 5: Effect of starch from the shoot of *Borassus aethiopum* on hematological parameters of the rats in sub-acute toxicity

	Mean±SEM			
Parameters	**Control**	**300 mg/kg**	**600 mg/kg**	**1200 mg/kg**
WBC (10^9/L)	4.69±0.82	5.12±1.76	4.40±0.82	5.92±0.46
RBC (10^{12}/L)	6.48±0.13	7.21±0.42	7.01±0.27	6.52±0.14
HGB (g/L)	9.16±0.16	9.75±0.48	10.13±0.22	9.83±0.19
HCT (%)	37.40±0.84	41.31±2.73	40.12±1.73	38.30±0.69

Values were presented as Mean ± SEM (n=6); one-way ANOVA. WBC, RBC, HGB, and HCT represent white blood cell count, red blood cell count, hemoglobin concentration, packed cell volume. P values indicate the level of significance; values less than 0.05 are significant and those greater than 0.05 are not significant at 5% level of probability.

Effects of oral administration of the starch of *Borassus aethiopum* on the body weights of the rat's in sub-acute toxicity

The absolute body weights of the rats recorded in the first, second, third and fourth weeks of the 28 days repeated oral dose toxicity study are shown in Table 6. There was a progressive increase in the daily body weight of the animals in both the treated groups and the control, which correlates to the normal growth in rats.

Table 6: Effects of oral administration of starch from *Borassus aethiopum* shoot on the total body weight

	Mean±SEM			
Weeks	**Control**	**300 mg/kg**	**600 mg/kg**	**1200 mg/kg**
First	104.10±16.97	86.80±11.97	119.90±11.00	83.22±12.43
Second	110.34±15.57	96.08±11.96	106.70±9.77	93.77±11.62
Third	115.88±14.95	108.45±10.52	118.72±8.45	101.93±11.73
Fourth	128.73±14.12	142.13±7.19	149.34±5.53	134.62±14.04

Values are presented as Mean ± SEM (n=6); one-way ANOVA. There were no statistically significant changes in the body weights of the treated group when compared with the control (P>0.05).

Effects of oral administration of the starch of *Borassus aethiopum* on the relative organ body weights of the rats in sub-acute toxicity

When different doses of the starch from the shoot of *B. aethiopum.* was orally administered for 28 days, there were no statistically significant changes in the relative organ body weights ratio of the liver, kidneys, heart and spleen of the treated group compared with the normal control (P>0.05), (Table 7).

Table 7: Effects of oral administration of starch from *Borassus aethiopum* shoot on the relative organ body weights of the rats in sub-acute toxicity

	Mean±SEM			
Parameters	**Control**	**300 mg/kg**	**600 mg/kg**	**1200 mg/kg**
Liver	5.58±0.68	5.58±0.68	5.76±0.20	5.65±0.26
Right kidney	0.55±0.08	0.56±0.02	0.57±0.02	0.59±0.03
Left kidney	0.51±0.07	0.58±0.04	0.59±0.03	0.57±0.03
Heart	0.68±0.03	0.68±0.04	0.66±0.01	0.65±0.02
Spleen	0.86±0.17	0.87±0.10	0.65±0.21	0.87±0.11

Values were expressed as Mean ± SEM (n=6); one-way ANOVA. No significant changes in the relative organ body weights ratio of the treated group compared with the control (P>0.05).

DISCUSSION

The preliminary scientific investigation of natural products for pharmacological effects are often accompanied by their toxicity evaluation. Medicinal plants prepared in different forms have been utilized for ages as therapeutic agents to alleviate human ailments on the assumption that they are safe and effective with little or no side effects. This has over time encouraged indiscriminate use of natural products as therapeutic agents without consideration to their toxic effects on the organ system of the body which could occur from chronic usage (Eran, et al., 2016). Some biomarkers were measured in this study to evaluate the toxic effects of starch from the shoot of *Borassus aethiopum* on certain organ systems functions especially on organs of excretion and metabolism. There are many reports on the potentials of *Borassus aethiopum* shoot starch as pharmaceutical excipients (Muazu *et al*., 2014).) but much knowledge about its toxicity is lacking which necessitate the need to scientifically investigate the toxicity of *Borassus aethiopum* in this study.

The oral acute toxicity (LD_{50}) of the starch was found to be greater than 4000 mg/kg with no mortality or any changes in gross behavior of the experimental animal. This finding is consistent with the article of Mohammad *et al* (2019) who also did not report mortality after 48 hours of observation. Furthermore, the result of the phytochemical screening of the ethanol shoot extract revealed the presence of alkaloids, tannins and carbohydrates which correlates to the report of (Issaka *et al*., 2016) where alkaloids and tannins were present.

Organ weight is also an important index of physiological and pathological status in animals (Dybing *et al*., 2002). because changes in organ and body weights can be indicators of adverse effects of drug or chemical. Again, the relative organ weight is fundamental to diagnose whether the organ was exposed to an injury or not. Significant alteration in organ body weight which could occur from organ atrophy or hypertrophy is an indication of adverse effects or damage caused by drugs and toxicants (Raza *et al.,* 2002). From the result, no significant changes were observed in the organ weights of the treated groups compared to the control. There was progressive increase in the body weights of both the treated and the control groups from the first to the fourth week. Macroscopically, no signs of inflammation or distortion in the appearance of the organs; liver, kidney, heart and spleen were observed. This revealed that the starch from the shoot of *B. aethiopum* did not affect the normal growth of the animal.

The liver as a major metabolic organ in the body often encounters insult from toxins found in ingested substances such as chemicals, drugs and environmental toxicants which can be harmful to the liver and equally affect its normal functions (Xi Yang *et al.,* 2014). Serum parameters are important biomarkers to identify the severity of tissue damage, possible target organs and to measure impaired organ functions (Syahirah *et al.,* 2018). Measurement of some biochemical parameters such as activities of enzymes have significant roles in disease pathology and organ toxicity (Malomo, 2000). An instance, increase in liver enzymes (AST, ALT, and ALP), is most often associated with hepatocellular damage; the results of these enzymes measurement and liver histology have been shown to be crucial for the assessment of hepatic injury in preclinical studies as an indicator of potential liability for hepatic injury in humans (Dufour, *et al.,* 2000; FDA, 2009). Alkaline phosphatase (ALP) usually assess the integrity of

plasma membrane. Increase in its serum level can be indication of increased synthesis of the enzyme in the presence of increasing biliary pressure which could suggest cholestasis (Hassan *et al.,* 2007).

This study revealed a significant decrease in ALP of the group treated with 600 and 1200 mg/kg doses of the extract which is contrary to the report of Muhammad *et al* (2018). Furthermore, a significant increase in AST and ALT were observed in the extract treated groups compared with the control. This finding is in agreement with the report of Muhammad *et al* (2018) which showed significant increase in AST and ALT at all doses. The significant increase in AST, ALT ($p<0.05$) and the AST/ALT ratio greater than 2:1 could suggest a harmful effect on the liver tissues, although Aspartate aminotransferase (AST) commonly used as a biomarker in hepatic injury is considered less specific for liver injury than ALT due to its expression from other tissues like the brain, myocardial cells and skeletal muscle cells. However, the ratio of AST to ALT helps in distinguishing between extra hepatic and hepatic injury, with an AST/ALT ratio greater than 2:1 being indicative of hepatic injury (Sharon & Gwaltney, 2016).

Furthermore, no significant changes in the values of the renal function parameters; sodium, potassium, chloride and urea in the treated groups at all doses of the extract compared with the control except a significant decrease in creatinine at the dose of 1200 mg/kg of the extract. Similarly, this study agreed with the findings of Muhammad *et al* (2018) at 25 and 50 % doses used except for the decrease in creatinine values. Creatinine as a metabolic waste of muscle metabolism is filtered and removed by the kidney in urine (Harita *et al.,* 2008). Therefore, the variations in serum biochemical parameters of the kidney did not suggested deleterious effects by the extract on renal function.

Haematological investigation of the shoots extract of *B. aethiopum* in the subacute study showed no significant alteration between the haematological parameters of the extract treated groups and the control. This implies that the ethanol crude shoots extract of *B. aethiopum* has not demonstrated effects that significantly improved or impaired the leucopoietic and hemopoietic systems. Haematological parameters can be used to detect the harmful effects mediated by the extract on blood components as indication of toxicity. For instance, significant decrease in blood Hgb, HCT and RBC concentration suggests anemia while a decrease in WBC count suggests immunosuppression and consequent decline in immune response to harmful foreign agents (Diallo, 2008; Syahirah *et al.,* 2018)

CONCLUSION

On the whole, the findings revealed presence of some biologically active constituents, no mortality or any noticeable changes in the general behaviour of the animals from the acute and subacute toxicities, no remarkable changes in the body and relative organ weight were observed. Similarly, no deleterious effects were observed on the renal function, haematological components and no sufficient evidence of hepatotoxicity. Therefore, the starch from the shoot of Borassus *aethiopum* has some evidence of toxicity on the liver from the subacute testing. Thus, there should be further investigation on the toxicity of the shoots of Borassus *aethiopum* because of its potential development into a pharmaceutical excipient.

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REFERENCES

Adamu, A., Muazu, J. and Madu S. (2015). Analysis of *Borassus aethiopum* shoot starch as a binder in a tablet formulation. European Journal of Biomedical and Pharmaceutical Sciences, 2(6): 20-26.

Das, N., Goshwami, D., Hasan, M., Sharif, R. and Zahir, S. (2015). Evaluation of acute and subacute toxicity induced by methanol extract of *Terminalia citrina* leaves in Sprague Dawlwy rats. 4(4): 316-321.

Denny, K.H. and Stewart, C.W. (2013). Acute, sub-acute, sub-chronic and chronic general toxicity testing for preclinical drug development. In: A Comprehensive Guide to Toxicology in Preclinical Drug Development. Elsevier Inc.: London; pp. 87-105

Diallo, A., Gbeassor, M., Vonor, A., Eklu-Gadegbeku, K. and Aklikokou, A. (2008). Effect of *Tectona grandis* on phenylhydrazine-induced anaemia in rats. Fitoterapia. 79(5): 332-336.

Dufour, D. R., Lott, J. A., Nolte, F. S., Gretch, D. R., Koff, R. S. and Seeff, L. B. (2000). Diagnosis and monitoring of hepatic injury, In: performance characteristics of laboratory tests. Clin Chem., 46(12): 2027-2049.

Dybing, E., Doe, J., Groten, J., Kleiner, J., O'Brien, J. and Renwick, A. G. (2002). Hazard characterization of chemicals in food and diet: dose response, mechanisms and extrapolation issues. Food and chemical toxicology, 40(2-3): 237-282.

Eran, B. A., Noah, S., Lee, H., Kamer, M., Suha, O. and Elad, S. (2016). Potential risks associated with traditional herbal medicine use in cancer care: A study of Middle Eastern oncology healthcare professionals. Cancer, 122(4): 598-610.

FDA (2009). FDA guidance for industry. Drug-induced liver injury. Premarketing clinical evaluation.www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064993.htm.

Fennell, C.W., Light, M. E., Sparg, S.G., Stafford, G.I. and Van Staden, J. (2004). Assessing African medicinal plants for efficacy and safety: Agricultural and storage practices. Journal of Ethnopharmacology. 95(2-3): 113-121

Harita, N., Hayashi, T. and Sato K. K. (2008). Lower Serum Creatinine in a New Risk Factor of Type 2 Diabetes. Journal of Biotechnology 6(8): 120-129

Hassan, S.W., Ladan, M.J., Dogondaji, R. A., Umar, R. A., Bilbis, L. S., Hassan, L. G., Ebbo, A. A. and Matazu, I. K. (2007). Phytochemical and Toxicological Studies of Aqueous Leaves Extracts of Erythrophleum africanum. Parkistan Journal of Biological Sciences 10(21): 3815-3821.

Issaka, J., Larbie, C. and Tancloh, M. A. (2016). Anti-diabetic effect of acqueous fruit extract of *Borassus aethiopum* (Mart.) in alloxan-induced diaabetic rats. International Journal of Phytomedicine. 8(3): 384-397.

Malomo, S. O. (2000). Toxicological implications of certriaxone administration in rats. Nigerian Journal of Biochemistry and Molecular Biology. 15(1): 33-38.

Merlin, L. K., Mensah, G. K., Arnold, D. F., Caleb F., Alexander K. A. and Rita A. D. (2019). Toxicity and Safety Implications of Herbal Medicines Used in Africa, Herbal Medicine, Philip F. Builders, https://www.intechopen.com/books

Muazu, J., Zakama, S. and Dzarmah, U. (2014). Extraction and characterization of the starch from the shoot of *Borassus aethiopum* as a prospective pharmaceutical raw material. World Journal of Pharmaceutical Sciences. 2(8): 704-710

Muhammad, S., Umar, K.J. and Hasan, S.W. (2019). Toxicity studies of African Palmyrah palm (*Borassus Aethiopum*) shoots. African Journal of Pure and Applied Chemistry. 13(2): 27-33.

Mussie, S. D., Kareru, P. G., Keriko J. M. and Berhane, G. N. (2015). Ethnobotanical Survey and Preliminary Phytochemical Studies of Plants Traditionally Used for Diabetes. Eritrea European Journal of Medicinal Plants. 9(2): 1-11.

Nasir, H. S. (2013). Toxicity and safety of medicinal plants. J Herb Med Pharmacol. 2(2): 21-22.

Newman, D.J. (2008). Natural products as leads to potential drugs: An old process or the new hope for drug discovery. J Med Chem. 51(9): 2589–2599.

OECD (2008). Guidelines for the testing of chemicals, Acute oral Toxicity-Up-and-Down-Procedure (UDP). 425, OECD.

OECD (2008). Repeated Dose 28-Day Oral Toxicity Study in Rodents.

Orwa, C. A., Mutua, K. R.., Jamnadass, R. and Anthony, S. (2009). Agroforestree Database:
a tree reference and selection guide version 4.0 (http://www.worldagroforestry.org/sites/treedbs/treedatabases.asp)

Rajasekar A, A. (2010). Characterization of corrosive bacterial consortia isolated from petroleum product transporting pipelines. Journal of Applied Microbiology and Biotechnology. 85(4): 1175-1188.

Raza, M., Al-Shabanah, O. A., El-Hadiyah, T. M. and Al-Majed, A. A. (2002). Effect of prolonged vigabatrin treatment on hematological and biochemical parameters in plasma, liver and kidney of Swiss albino mice. Sci Pharm.70: 135-145

Sharon, M. and Gwaltney, B. (2016). Nutraceuticals in Hepatic Diseases. In Nutraceuticals (pp. 87–99). Elsevier. https://doi.org/10.1016/B978-0-12-802147-7.00007-3

Sofowora, E. (1989). Medicinal plants and traditional medicine in Africa (Vol. 1st edition). Ibadan: Spectrum Books Ltd.

Sofowora, E. (1993). Medicinal Plants and Traditional Medicine in Africa (2nd Edition ed.). Ibadan, Nigeria: John Wiley and Sons Ltd.

Syahirah, A., Sayuti, N., Hamzah, H., Rosly, S. M., Farhan, H. R. M., Mohamed M. N. and Norhaizan, M. E. (2018). Subacute Oral Toxicity Assesment of Ethanol Extract of *Mariposa christia vespertilionis* Leaves in Male Sprague Dawley Rats. Toxicological Research 34(2): 85−95

Tasneef, A., Swatantra, B. S. and Shivshankar, P. (2013). Phytochemical screening and physicochemical parameters of crude drugs: A brief review. International Journal of Pharma Research. 2(12): 53-60.

Xi Yang L. K., Schnackenberg, Q, S. and William, F. S. (2014). Hepatic toxicity biomarkers in: R. Gupta (Ed): Biomarkers in Toxicology. Elsevier Inc. pp 214-259

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