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Assessment of the Oral Safety Profile of Aqueous and Hexane Root Extracts of African Laburnum (*Cassia sieberiana* Dc.) in Albino Rats

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ABSTRACT

Cassia sieberiana, primarily found in Africa, particularly in Nigeria, has been an analgesic, antibiotic, and anti-inflammatory agent for decades. However, a scientific evaluation investigation is underway to assess its safety and efficacy. The present study evaluated the safety of aqueous and hexane root extracts of *C. sieberiana in* albino rats. The LD_{50} and sub-chronic toxicity were determined using (OECD method to assess the effect of the extracts on kidney and liver parameters after 28 days of oral administration of 1000, 2000, 3000, and 4000 mg/kg B.W. The result indicated that the LD_{50} of the extract was >5000 mg/kg B.W. The aqueous extract significantly ($P<0.05$) decreased total bilirubin, whereas no significant change ($P>0.05$) was observed in AST, ALP, albumin, and TP when compared with the control. Significant ($P<0.05$) increases in ALP and albumin at doses of 4000 and 3000 mg/kg, respectively, were observed in the group administered hexane extract. Dose-dependent increase ($P<0.05$) in creatinine was observed in the group administered hexane extract. However, there were no significant changes ($P<0.05$) in kidney function parameters and electrolytes in rats administered the aqueous extracts. Moreover, all rats exhibited normal increases in body weight. These results indicated that the aqueous extract is nontoxic, whereas the hexane extract showed significant changes in liver function parameters at high doses in healthy albino rats; hence, the extracts can be considered safe for consumption at administered doses.

Keywords: *C. siberiana*, aqueous extract, hexane extract, LD_{50}, subchronic toxicity

INTRODUCTION

Medicinal plants are fundamental sources of medicine that play an integral role in the management of a variety of diseases (Ahmad *et al*., 2019; Jamal, 2023). Many countries worldwide depend on medicinal plants for primary health care because of their cultural acceptability, affordability, availability, and minimal side effects (Akah, 2008; Fayiah *et al*., 2023). Regardless of the importance of these plant products, there are uncertainties regarding their safety profile, especially in terms of poor detectable signs of toxicity (Ya'u *et al*., 2013). The toxicity may be a result of overdosage of these plants because there is no standardized dosage system in traditional medical practice (Erinoso, 1998). This brings about an evaluation of the short and long-term use of such medicinal plants (Birdi *et al*., 2010).

Cassia sieberiana DC. (Caesalpiniaceae) is widely distributed in the Southern Sahel and Sudan Savanna from Senegal, Uganda, and Nigeria (Micheal, 2004, Von Maydell, 1990). The common name is African laburnum or drumstick tree (English), and the Indigenous names in Nigeria include "marga" in Hausa, "margaje" in Fulani, "kiskatigrai" in Kanuri, and "ifo" or "aridantooro" in Yoruba (Keay, 1989; Mohammed, 2019). Ethnomedically, the aqueous extracts of the roots, stem bark, and fruit pulp have been traditionally used in northeastern Nigeria for the treatment of inflammatory conditions, tiredness, and joint pains (Modusolumuo *et al.*, 1999). The extracts are used to treat fever, malaria, diarrhea, leprosy, bilharzias, and stomach pain and as a diuretic and dewormer (Gledhill, 1991; Tamboura *et al*., 2005). The decoction of the root is used with other plants as a sex stimulant (aphrodisiac).

However, medicinal plants should not only be effective in the treatment and management of diseases but also be safe for consumption. Therefore, this research work is aimed at determining the acute and subchronic toxicity of the aqueous and hexane root extracts of *Cassia siberiana.*

MATERIALS AND METHODS

Plant Collection and Identification

Cassia sieberiana (roots) was obtained from Dajin Adarawa, Wamakko Local Government, Sokoto State, Nigeria. The plant species was authenticated by a taxonomist in the Botany unit, Biological Science Department, Usmanu Danfodiyo University, Sokoto, and voucher specimens (UDUS/ANS/0235) were deposited.

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Preparation of Plant Extracts

The preparation of the extract was carried out according to the method of Hassan *et al.* (2013). The roots of *C. sieberiana* were cleaned with distilled water, shade-dried at room temperature in the laboratory, and ground to a powder using a pestle and mortar. Equal amounts of the dried powder (500g) were macerated separately using 2 L of normal hexane and 2 L of distilled water for 72 h, and the resulting mixture was filtered with muslin cloth first and then with filter paper Whatman No. 1. The filtrates were then filtered with a clean muslin cloth, and the filtrates were concentrated at 40^0C and then evaporated to dryness at 45 ^{0}C using rotary evaporator (model RE – 52A). The dried extracts were stored in plastic containers and maintained at room temperature until needed for analysis.

Experimental animals

Healthy male and female rats (*Rattus norvegicus*), 2–2.5 months old, weighing between 180–200 g, and female, 1.5–2 months old, weighing between 155–165, were obtained from the animal house, Usmanu Danfodiyo University Sokoto, Nigeria. The animals were kept in well-aerated laboratory cages in well-ventilated rooms under supervision in the animal house with free access to feed (Vital Agricultural Feed Nigeria Ltd) and water *ad libitum*. The animals were kept in the same environment for two weeks to acclimatize.

Acute Oral Toxicity Study

The acute oral toxicity study was conducted according to the method of the Organization for Economic and Cultural Development (OECD, 2001). Ten albino rats (five each for aqueous and hexane extract) were randomly selected and used in the experiment. The extract was administered to each albino rat at a single oral limit test dose of 5000 mg/kg body weight. After administration, food was withheld for a further 3–4 h and was observed individually at least once during the first 30 min after dosing, periodically at 8, 14, 24, and 48 h intervals with special attention during the first 4 h. The observations included hair loss, loss of appetite, drowsiness, salivation, tremors, and convulsions. The rats were thereafter observed for 14 days for signs of delayed toxicity.

Sub-chronic Oral Toxicity Studies

The sub-chronic oral toxicity test was performed according to the Organization of Economic Co-operation and Development guideline 407 for the testing of chemicals (OECD, 2008). Thirty-six rats were distributed into nine (9) groups of 4 rats each. Groups II to V received graded doses of the aqueous extract (1000, 2000, 3000, and 4000) daily for 28 days, whereas rats in groups VI to IX received graded doses of the hexane extract (1000, 2000, 3000, and 4000) daily for 28 days. Rats in group I served as the control group and received distilled water for the test period. The body weights of all rats were recorded before and during the treatment period weekly.

Liver and Kidney Function Test

Rats used for sub-chronic oral toxicity were decapitated, and blood collected from individual rats was centrifuged to obtain sera. The sera were used for biochemical estimations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin (ALB), total protein (TP), and total bilirubin (TB) for liver function indices. Serum samples were also used for biochemical estimations of creatinine, uric acid, urea, Na^+, $K^{+,}$ and Cl^- for kidney function indices.

Statistical Analysis

All data are presented as mean ± Standard Error of Mean (SEM). Values were analyzed using the Instat software (Version U.S.A). The statistical significance of differences between means was determined using one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test. $P<0.05$ was considered statistically significant.

RESULTS

Acute Oral Toxicity Study

Single oral administration of 5000 mg/kg of *C. sieberiana* root to albino rats did not produce any visible or clinical signs of toxicity or mortality in the treated rats. Behavioural changes such as weakness, bulging of the eye, hair loss, salivation, and food and water refusal were not observed for over 14 days. Thus, the result indicates that the LD_{50} of both the aqueous and hexane root extracts of *C. siberiana* is greater than 5000 mg/kg.

Effect of Oral Administration of Aqueous and Hexane Root Extract of *C. siberiania* on Body Weights of Rats

The effect of oral administration of aqueous and hexane root extracts of *C. sieberiana* on body weight changes in rats is shown in Table 1. A significant increase in the body weight of rats in the control group was observed at weeks 2, 3, and 4 compared with the initial weight at week 0. A gradual increase in body weight was not statistically significant ($p>0.05$) in rats administered all the experimental doses.

Table 1: Effect of Oral Administration of Aqueous Root Extract of *Cassia sieberiana* on the Body Weight of Rats (mg/kg)

Week	Control	1000	2000	3000	4000
0	140.25±1.11	135.75±2.85	148.75±0.65	145.50±0.41	142.25±0.65
1	142.75±1.55	136.00±0.41	149.50±1.44	145.00±0.29	141.75±0.48
2	145.50±3.16*****	137.25±1.75	150.25±1.38	146.25±1.48	142.50±0.96
3	147.25±2.85*****	138.00±3.71	151.25±0.48	146.75±2.40	144.00±0.41
4	150.25±0.41*****	140.75±2.25	151.75±1.14	148.00±0.41	145.00±0.48

Values are Mean ± SEM. * $P<0.05$ = significantly different when compared to their initial weight down the column.

Table 2: Effect of Oral Administration of Hexane Root Extract of *Cassia sieberiana* on Body Weight of Rats (mg/kg)

Week	Control	1000	2000	3000	4000
0	140.25±1.11	151.75±0.85	147.00±0.65	145.50±0.41	137.25±0.65
1	142.75±1.55	152.75±0.75	147.75±0.28	146.00±0.29	137.75±0.48
2	145.50±3.16*****	153.00±0.41	148.25±1.44	146.75±0.48	138.75±0.41
3	147.25±2.85*****	153.75±0.25	148.75±0.48	147.75±0.41	139.50±0.96
4	150.25±0.41*****	154.00±0.71	149.00±1.38	148.00±0.48	140.00±0.48

Values are Mean ± SEM (n= 4). *$P<0.05$: significantly different when compared to their initial weight down the column

Effect of Oral Administration of Aqueous and Hexane Root Extracts of *C. sieberiana* on Liver Function in Rats

The effects of aqueous and hexane root extracts of *C. sieberiana* on liver function in albino rats are shown in Tables 3 and 4, respectively. The aqueous extract at 4000 mg/kg significantly ($p < 0.05$) lowers the level of total bilirubin compared with the control. No significant effect ($p>0.05$) was observed in aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin (ALB), and total protein TP when compared with the control. The hexane extracts significantly ($p<0.05$) increased alkaline phosphatase (ALP) activity and albumin (ALB) levels at doses of 4000 and 3000 mg/kg, respectively, as compared with the control, whereas no significant ($p>0.05$) change was observed in ALT, AST, and TB when compared with their respective control.

Table 3: Effect of oral administration of aqueous root extracts of *Cassia sieberiana* on Liver Function in Rats

Dose (mg/kg)	ALT (U/L)	AST (U/L)	ALP (U/L)	ALB (g/dl)	TP (g/dl)	TB (mg/dl)
0	40.25±0.85	139.25±3.52	234.75±4.05	3.03±0.19	5.24±0.25	1.07±0.08
1000	41.50±0.85	141.50±2.72	235.75±3.04	2.90±0.22	5.25±0.63	0.99±0.02
2000	39.25±0.63	142.20±2.55	326.50±4.05	2.98±0.03	5.20±0.14	0.84±0.09
3000	38.50±1.04	143.50±1.19	237.25±7.43	3.15±0.12	5.23±0.08	0.80±0.06
4000	38.00±0.91	147.00±2.19	241.50±3.86	3.10±0.14	5.73±0.17	0.78±0.05*****

Mean± SEM (n= 4). * = Significantly different from the control ($P < 0.05$) down the column. AS, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; ALB, albumin; TP, total protein; TB, total bilirubin

Table 4: Effect of oral administration of hexane root extract of *Cassia sieberiana* on Liver Function in Rats

Dose (mg/kg)	ALT (U/L)	AST (U/L)	ALP (U/L)	ALB (g/dl)	TP (g/dl)	TB (mg/dl)
0	40.25±0.85	139.25±3.52	234.75±4.05	3.03±0.19	5.24±0.25	1.07±0/08
1000	42.75±1.80	137.25±0.48	232.00±4.95	3.30±0.16	6.20±0.17	1.13±0.09
2000	41.25±0.85	136.75±0.85	242.50±1.50	3.18±0.11	6.10±0.12	1.01±0.05
3000	41.75±0.63	135.50±1.32	243.25±6.07	3.65±0.11*****	6.00±0.12	0.96±0.04
4000	38.50±1.94	132.50±3.22	252.25±3.45*****	3.20±0.10	6.20±0.12	0.94±0.16

Values are Mean± SEM (n= 4). * = Significantly different from the control (P<0.05) down the column. AST, aspartate amino transferase; ALT, alanine amino transferase; ALP, alkaline phosphatase; ALB, albumin; TP, total protein; TB, total bilirubin

Effect of Oral Administration of Aqueous and Hexane Root Extracts of *C. sieberiana* on Kidney Function in Rats

The effects of aqueous root extracts of *C. sieberiana* on kidney function in albino rats are shown in Tables 5 and 6, respectively. There was no significant difference (P>0.05) observed for the indices of kidney function (urea, creatinine, uric acid) and electrolytes (sodium, potassium, and chloride ions) in rats administered the aqueous extracts compared with the control group. A significant (P<0.05) increase in creatinine of the group administered with 4000 mg/kg of the hexane extract was observed compared with the control.

Table 5: Effect of Oral Administration of Aqueous Root Extract of *Cassia sieberiana* on Kidney Function in Rats

Doses	CRT	Urea	UA (mg/dl)	Na^+ (mmol/l)	K^+	Cl^-
0	1.28±0.05	5.40±0.18	1.48±0.12	152.50±0.87	5.18±0.17	105.25±1.38
1000	1.15±0.09	5.50±0.07	1.38±0.05	153.50±6.06	4.90±0.19	104.50±2.06
2000	1.07±0.05	5.35±0.10	1.49±0.13	141.00±3.32	5.00±0.08	98.25±1.49
3000	0.98±0.11	5.10±0.13	1.50±0.11	147.00±1.29	5.83±0.21	103.25±2.14
4000	0.98±0.71	4.80±0.35	1.45±0.06	145.50±1.89	5.70±0.22	100.75±0.95

Values are Mean ± SEM (n= 4). Values were not significantly different down the column
Key: CRT- Creatinine, UA- Uric Acid, Na^+- Sodium ion, K^+- Potassium ion, Cl^-- Chloride ion

Table 6: Effect of oral administration of hexane root extract of *C. sieberiana* on Kidney Function in Rats

Doses	CRT (mg/dl)	Urea	UA (mg/dl)	Na^+ (mmol/l)	K^+	Cl^-
0	1.28±0.05	5.40±0.18	1.48±0.12	152.50±0.87	5.18±0.17	105.25±1.38
1000	1.30±0.04	5.75±0.14	1.42±0.08	157.00±2.27	5.30±0.33	107.00±1.47
2000	1.28±0.05	6.03±0.18	1.51±0.07	149.75±3.77	5.15±0.13	103.25±1.49
3000	1.08±0.08	5.80±0.08	1.44±0.04	147.50±1.55	5.45±0.10	105.50±2.22
4000	0.91±0.06*****	5.30±0.13	1.30±0.07	147.00±2.38	5.60±0.32	105.25±1.49

Values are Mean± SEM (n= 4). * = Significantly different from the control down the column (P<0.05)
Key: CRT- Creatinine, UA- Uric Acid, Na^+- Sodium ion, K^+- Potassium ion, Cl^-- Chloride ion

DISCUSSION

Acute toxicity studies may provide fundamental information on the mode of toxic action of an agent, act as the basis for classification and labelling, and help in deciding the dose of novel compounds in animal studies substance (Zahran *et al*., 2019). Moreover, if a high dose (e.g., 5000 mg/kg) is found to be survivable, no further acute testing will be conducted (NRC, 2006). This study showed that the LD_{50} of the aqueous and hexane root extract of *C. sieberiana* was greater than 5000 mg/kg, indicating that it is essentially non-toxic at an "acute dose". The results of the present study support previous data from Evenamede *et al.* (2019), who evaluated the toxicity of hydroethanolic extracts of the root and stem barks of *C. sieberiana* D.C. on Wistar rats.

In this study, after 28 days of treatment with the extract of *C. sieberiana*, all rats exhibited a normal increment in body weight. Body weight changes serve as a sensitive indication of the general health status of animals (Teo *et al*., 2002). Significant changes in the body weights of animals are important indicators of the adverse effects of drugs and chemicals (Teo *et al*., 2002). Hence, the extract of *C. sieberiana* did not affect the normal metabolism of the experimental animals.

Serum alanine aminotransferase (ALT) is a cytoplasmic enzyme found in very high concentrations in the liver and kidney, with skeletal muscles having less enzyme activity (Ahmed, 2015). An increase in the activity of this enzyme indicates hepatocellular damage (Wang *et al*., 2012). Serum aspartate aminotransferase activity (AST) is located in the microsomal and mitochondrial portions of liver cells, skin, skeletal and cardiac muscles, pancreas, and kidney (Hayashi *et al*., 2003; McDaniel, 2019). Aspartate aminotransferase activity (AST) is less specific than ALT as an indicator of liver function, and

ALT activity is usually greater than AST activity in early or acute hepatocellular disease (Ahmed, 2015). Although both are useful indices for identifying inflammation and necrosis of the liver (McDaniel, 2019). Serum alkaline phosphatase (ALP) levels are increased in many clinical states; bone and liver diseases are the most important (McDaniel, 2019). An increase in ALP activity in liver disease is as a result of increased synthesis of the enzyme by cells lining the bile canaliculi, usually in response to cholestasis, which may be intra or extra-hepatic (Sultan *et al.*, 2019).

The insignificant change in liver function indices of rats administered the aqueous extract may indicate its safety to the liver. However, the significant increase observed in the ALP activity of rats administered 4000 mg/kg of the hexane extract may be due to its ability to extract more toxic constituents of the roots than the aqueous solvent. Serum ALP is a useful diagnostic, screening, and follow-up tool for cholestatic, hepatobiliary, and osteoblastic bone diseases (Sultan *et al.*, 2019). Cholestasis is the main, if not the only, liver disease responsible for increased plasma alkaline phosphatase activity. Likewise, the elevation of serum ALP activity may be due to increased functional activity of the liver, probably leading to *de novo* synthesis of the enzyme molecules (Yakubu *et al*., 2005). Thus, increased alkaline phosphatase activity in the presence of normal levels of other liver function parameters may be suggestive of liver pathology other than obstruction (McDaniel, 2019). In contrast, Obidah *et al*. (2009) reported that oral administration of the stem bark extract of *C. sieberiana* to rats resulted in a significant increase in ALT and AST levels.

A decrease in albumin and total proteins is a sign of reduced synthetic ability of the liver or might be due to impaired hepatocellular function (Levitt and Levitt, 2016). The albumin-to-globulin ratio shows a sharp decline during hepatocellular injury. According to Levitt and Levitt (2016), serum albumin and total proteins are usually measured to evaluate the synthetic capacity of the liver. Low serum albumin content suggests infection or continuous loss of albumin (Yakubu *et al*., 2003; Levitt and Levitt, 2016). Malnutrition also causes depletion of these proteins in the serum (Oluwole *et al*., 2012). In this study, no significant difference was observed between the groups administered the aqueous extract. However, a significant increase in albumin was observed among the groups treated with 3000 mg/kg of the hexane extract, which may help in preventing oxidative damage to the liver. Increases in albumin and total protein have a hepatoprotective effect (Oyagbemi *et al*., 2008).

Bilirubin is a useful indicator of the excretory function of the liver and is used to assess haemolytic anaemia (Kubilay *et al*., 2016). It is a breakdown product of haemoglobin and is assayed to measure the binding, excreting, and conjugating ability of a hepatocyte (Onu *et al*., 2013). A decrease in serum bilirubin occurs in a bimodal fashion when biliary obstruction is resolved (Alvarez, 1999; McDaniel *et al*., 2019). The significant decrease observed in the group administered with 4000 mg/kg of the aqueous extract may be due to the ability of the extract to exert curative action at higher doses. This, however, is in contrast with the report of Donkor *et al*. (2014), who showed elevated levels of total bilirubin in animals treated with the aqueous extract *of C. sieberiana* root bark for 3 months compared with the control.

Serum urea, creatinine, and uric acid assays are usually used to assess normal kidney function (Stewart *et al*., 2018). Urea and uric acid are the major nitrogen-containing metabolic end products of protein and purine catabolism, respectively (Wright, 1995; Stewart *et al*., 2018). Creatinine is a waste product of muscle energy metabolism (Baracho *et al*., 2015). They are found in the liver and are conveyed through the blood and kidneys for excretion (Oluwole *et al*., 2012). Healthy kidneys remove these compounds from the blood to be excreted in the urine (Baracho *et al*., 2015). Elevation of these metabolites in the blood is an indication of renal dysfunction (Cotran *et al*., 2005; Stewart *et al*., 2018). Nephrotoxicants increase, whereas nephroprotective agents reduce serum urea and creatinine levels in rats (Abdel-Moneim *et al.*, 2007). Therefore, it may be inferred that the extracts used in this study are not nephrotoxic.

The levels of electrolytes in the blood are the outcome of the fine regulatory mechanism of ionic charges and osmotic balance (Ashish *et al*., 2006; Idoko *et al*., 2018). According to McKinley and Johnson (2004), the "optimum state of equilibrium is achieved by an interplay involving the kidney, lungs, and endocrine system". Significant alteration in the concentration of serum electrolytes such as sodium, potassium, bicarbonate, and chloride is indicative of poor renal function or renal impairment (Stewart *et al*., 2018). Increased sodium in the blood may result from kidney disease, too little water intake, and loss of water due to diarrhoea and vomiting (Conrad, 2012; Stewart *et al*., 2018). A decrease in sodium levels results from a relative increase in the amount of body water relative to sodium (Ashish *et al*., 2006). The potassium ion is a cation of the intracellular fluid that plays a vital role in muscle contraction (Manoj and Stephen, 2012). It is

normally excreted by the kidney; hence, disorders that impair kidney function can lead to hyperkalemia (Enemor and Okaka, 2013). The insignificant change observed in the study could be attributed to normal kidney function.

The bicarbonate buffer system is the most important among blood buffers when the pH of the blood is considered (Hastings and Bowker, 2018). Chloride ions are major extracellular anions (Arneson, 2014) and are involved in maintaining proper water distribution, osmotic pressure, and normal acid- base balance in the extracellular fluid compartment (Soetan *et al*., 2010; Hastings and Bowker, 2018). From the results of the present study, it may be inferred that the acid-base balance of the rats was not affected by the administration of the aqueous and hexane extracts.

CONCLUSION

The findings of this study indicate that the extract of *Cassia sieberienna* is safe for consumption at administered doses

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