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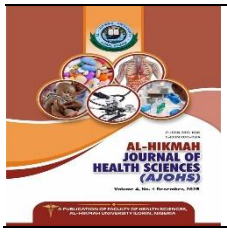

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Original Article

Toxicological and Biochemical Assessment of Aqueous *Chromolaena odorata* (Siam Weed) Extract on Hepatorenal Function in Wistar Rats

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ABSTRACT

Objective: This study investigated the hepatorenal function of the aqueous extract of *Chromolaena odorata* in male Wistar rats.

Materials and Methods: The study employed a control experimental design with 29 healthy male Wistar rats weighing 120±20 g. After one week of acclimatization, the test groups were given aqueous extract of *Chromolaena odorata* leaf in addition to a normal diet for 14 days. At the end of the experiment, the rats were anesthetized and sacrificed via heart puncture, and the blood was collected into a plain bottle for biochemical analysis. Urea was estimated by Berthelot's method, while creatinine was estimated by Jaffe's reaction method. Liver enzyme activities were assessed using the colorimetric method, while the Jendrassik-Groff, Bromocresol Green, and Biuret methods were used to measure bilirubin, albumin, and total protein, respectively.

Results: The biochemical results showed significantly ($p<0.05$) lower levels of total protein and albumin and increased levels of urea, creatinine, bilirubin, and liver enzyme activities with an increase in concentrations of the aqueous extract of *Chromolaena odorata.*

Conclusion: This study showed that the aqueous extract of *Chromolaena odorata* significantly alters the renal and hepatic profiles, suggesting that it may have adverse effects on kidney and liver function, especially at higher concentrations. Thus, the toxicological effect of the extract is dose-dependent.

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Introduction

Globally, many traditional medicinal herbs and plant parts (leaves, stems, roots, and bark) are effective in rural healthcare and disease prevention (Ezeigbo *et al*., 2016). Pharmacologically important phytochemicals found in plants include alkaloids, essential oils, flavonoids, tannins, terpenoids, saponins, and phenolic compounds, which can be used to treat a variety of diseases (Omeke *et al*., 2019). One of the commonly used plants is *Chromolaena odorata (C. odorata),* a tropical and subtropical flowering shrub in the sunflower family (Anyanwu *et al*., 2017). It is native to North America, particularly Florida and Texas, as well as Mexico and the Caribbean, but it has spread to South America, Tropical Asia, West Africa, and parts of Australia (Anyanwu *et al*., 2017). It is a fast-growing, abundant, and widespread perennial scandent or semi-woody flowering shrub from the sunflower family *Asteraceae* (Odutayo *et al.*, 2017).

C. odorata is known by many names, including Siam weed, Christmas bush, devil weed, camfhur grass, and common floss flower (Lalith, 2009). In Nigeria, *C. odorata* is commonly known as Ewe Awolowo, Siam weed, Elizabeth weed, Obirakara, Olorohuru, and independent weed (Anyanwu *et al.,* 2017). *C. odorata* is used extensively in Nigeria for soil fertility improvement as well as for medicinal (Uyi *et al*., 2014) and ornamental purposes. The plant is also popularly used for wound healing due to its antimicrobial properties (Odugbemi, 2006). The anthelmintic properties of the aqueous extracts of *C. odorata* have also been widely known among the rural populations of Africa. Several studies have shown that *C. odorata* is an effective treatment for diarrhea, malaria, toothache, diabetes, skin diseases, dysentery, and colitis (Akinmoladun & Akinloye, 2007; Anyanwu *et al*., 2017).

The medicinal properties of *C. odorata* are attributed to specific phenolic compounds that have been isolated from it; however, *C. odorata* also contains a carcinogenic substance known as "pyrrolizidine alkaloids" (Fu *et al*., 2002).

C. odorata is toxic to cattle and may cause allergic reactions (Lalith 2009). The human kidneys and liver are both vital organs in the body. The human liver metabolizes xenobiotics, while the kidneys are responsible for ultrafiltration and metabolic waste excretion, among other functions. The liver and kidneys are, therefore, susceptible to toxicity from various toxic agents. Chemicals and herbal remedies can induce damage to these organs. Thus, this study investigated the effects of an aqueous extract of *C. odorata* on the liver and kidney of Wistar rats.

Materials And Methods

Study Area

The study was conducted at the animal house of the Department of Medical Laboratory Science, Al-Hikmah University, Ilorin, Kwara State.

Study Design

A control experimental study with twenty-nine (29) healthy male Wistar rats was conducted at the Animal House of the Department of Medical Laboratory Science, Al-Hikmah University, Ilorin, Kwara State, Nigeria.

Experimental Animals

Twenty-nine healthy male albino rats of the Wistar strain, at least 8 weeks old, weighing 120±20 g, were purchased from Al-Hikmah University Animal House. The rats have been domesticated for purely scientific experiments (Krinke, 2000) and serve as important animal models for research in both biomedical sciences and psychology (Vandenbergh, 2000) The animals were allowed to acclimate for seven days, well fed, and maintained in a clean cage located in a well-ventilated room with controlled environmental conditions of 12 hours of light/day cycle, a temperature of 21-31^{0}C and a relative humidity of 45-55%.

Plant Collection and Identification

Fresh *C. odorata* leaves were collected within the Ilorin municipality, Kwara State, Nigeria. The plant was identified and authenticated at the herbarium unit of the Department of Plant Biology, Faculty of Life Sciences, University of Ilorin, Kwara State, where it was given the herbarium voucher number UILH/001/1356/2022 and deposited in the herbarium.

Preparation of Plant Aqueous Extract

The fresh *C. odorata* leaves were shade-dried at room temperature for ten days, then ground using an industrial blender. The stock aqueous extract was obtained by adding 12 mL of double-distilled water to a 250 mL beaker in a magnetic stirrer for 10 minutes, after which we added 60 mg of air-dried and milled plant material. Then, the mixture was continuously stirred at 60°C for 15 minutes. The extract obtained was passed through a Whatman filter to remove particulate matter. Finally, the extracts were stored in the refrigerator at 4°C to be used in the future (Daisy & Saipriya, 2012).

Administration of Extract

In this study, acute and subchronic toxicities were investigated, and all animal groups were treated humanely by being provided with a rat diet and water.

Acute toxicity study

The acute oral toxicity study and limit test were carried out in accordance with the guidelines established by the Organization for Economic Cooperation and Development (OECD, Limit Test, 423) (OECD, 2001). The acute toxicity group was divided into three groups:

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control, 2000 mg/kg, and 5000 mg/kg, respectively. The extract was administered intragastrically to rats in groups 2 and 3 once daily, starting with group 2, in oral doses of 2000 mg/kg and 5000 mg/kg body weight. The animals were observed for toxic symptoms within the first four hours and then again after 24 hours. Also, the behavioral parameters and mortality rates were closely monitored for 14 days.

Table 1

Group	Species	Treatment	Number of animals
Control	Rats	Rat chow and water	3
Test group administered with 2000mg/Kg	Rats	Rat chow + water + 2000mg/kg extract	3
Test group administered with 5000mg/Kg	Rats	Rat chow + water + 5000mg/kg extract	3

Sub-chronic Toxicity study

Twenty male Wistar rats were randomly assigned to four groups of five rats each, in accordance with OECD 407 guidelines (OECD, 2001). Group 1 was the control group, which was given only rat chow and distilled water. Groups 2, 3, and 4 were given graded doses of the aqueous extract orally, at 500 mg/kg, 1000 mg/kg, and 1500 mg/kg, respectively, daily for 14 days. Throughout the experiment, all rats were given free access to food and water, and they were monitored daily for general signs of toxicity and mortality.

Table 2

Group	Species	Treatment	Number of animals
Control	Rats	Normal rat chow and water	5
Test group administered with 500mg/Kg	Rats	Normal rat chow and water + 500mg/kg	5
Test group administered with 1000mg/Kg	Rats	Normal rat chow and water + 1000mg/kg	5
Test group administered with 1500mg/Kg	Rats	Normal rat chow and water + 1500mg/kg	5

All rats had access to rat feed and water throughout the study and were observed daily for signs of toxicity and mortality. At the end of the feeding period, the animals were sacrificed, and a blood sample was collected for analysis.

Blood Sample Collection and Processing

At the end of the experiments, the rats were anaesthetized with chloroform inhalation and euthanized. Blood samples were collected by heart puncture from each of the rats into well-labeled dry-plain tubes for biochemical analysis. The blood samples were allowed to clot. They were spun at 12,000 g for 15 minutes. The serum of the blood samples was separated into different well-labeled dry-plain tubes before analysis. The serum was quantitatively estimated for liver enzyme activities, total protein, bilirubin, albumin, urea, and creatinine.

Laboratory Analysis

The biochemical analysis was conducted at Al-Hikmah University's Chemical Pathology Department in Ilorin. The levels of urea, creatinine, liver enzyme activity, total protein, bilirubin, and albumin were measured spectrophotometrically in the separated plasma.

Alanine Aminotransferase (ALT) Enzyme Activity Was Determined Using the Colorimetric Method Modified by IFCC (1990).

Principle: Alanine aminotransferase catalyzes the transfer of amino groups from Alanine to oxoglutarate with the formation of glutamate and pyruvate. The latter is reduced to lactate dehydrogenase in the presence of reduced nicotinamide adenine dinucleotide (NADH).

$$\text{I-oxoglutarate + L-alanine} \xrightarrow{\text{ALT}} \alpha\text{-L-glutamate + Pyruvate}$$

$$\text{Pyruvate + NADH + H}^+ \xrightarrow{\text{LD}} \text{L-lactate + NAD}^+$$

Aspartate Aminotransferase (AST) Enzyme Activity Was Assayed by Colorimetric Method (IFCC, 1990)

Principle: Aspartate aminotransferase catalyzes the transfer of the amino group from aspartate to

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α-ketoglutarate with the formation of glutamate and oxaloacetate. The latter is reduced to malate-by-malate dehydrogenase (MDH) in the presence of reduced nicotinamide adenine dinucleotide (NADH).

AST
α-ketoglutarate + L-aspartate ⟶ L-glutamate + Oxaloacetate

MDH
Oxaloacetate + NADH + H^+ ⟶ L-malate + NAD^+

Alkaline phosphatase enzyme activity was assayed by the colorimetric method modified by IFCC (1990)
Principle: Alkaline phosphatase hydrolyzes *p*-nitrophenyl phosphate to *p*-nitrophenol and phosphate. The phosphate is transferred to AMP (2-Amino-2-methyl-1-propanol) The increase in absorbance at 405 nm at 37 °C is measured and proportional to the amount of alkaline phosphatase present in the sample.

ALP
p-nitrophenylphosphate + H2O -------> Phosphate + p-nitrophenol

Quantitative Estimation of Bilirubin by Colorimetric Method (Jendrassik-Groff, 1938)
Principle: Direct (conjugated) bilirubin reacts with diazotized sulphanilic acid in an alkaline medium to form a blue-colored complex. Total bilirubin is determined in the presence of caffeine, which releases albumin-bound bilirubin, by the reaction with diazotized sulphanilic acid.

Total bilirubin:
Sulfanilic acid + NO_2^- -----> Diazo Salt + Bilirubin---------> Azobilirubin (600nm)

Direct bilirubin:
Sulfanilic acid + NO_2^- ---------> Diazo Salt + Bilirubin----------> Azobilirubin (550nm)

Quantitative Estimation of Albumin by Bromocresol Green Method (Bartholomew and Delaney, 1966)
Principle: The measurement of serum albumin is based on its quantitative binding to the indicator 3, 3', 5, 5'-tetrabromo cresol sulphonephthalein (bromocresol green, BCG). The albumin-BCG complex absorbs maximally at 630 nm; the absorbance is directly proportional to the albumin concentration in the sample.

Total Protein Estimation using the Biuret method described by Bartholomew and Delaney (1966)
Principle: Cupric ions, in an alkaline medium, interact with protein peptide bonds, resulting in the formation of a colored complex.

Quantitative Estimation of Serum Creatinine by Modified Jaffe's Method (Jaffe, 1886)
Principle: Creatinine in an alkaline solution reacts with picric acid to form a colored complex. The amount of the complex formed is directly proportional to the creatinine concentration measured at 520 nm.

Serum Urea Estimation by Urease Berthelot Method (Weatherburn, 1967)
Principle
Salicylate and hypochlorite in the reagent react with the ammonium ions to form a green complex (2,2-dicarboxylindophenol). The estimation procedure of serum urea is based on the following reaction:
Urea + $H_20 \rightarrow 2NH_3 + C0_2$

Data Analysis
The data obtained were analyzed using IBM SPSS Statistics software Version 23. The measured data were expressed as mean ± SEM. Group comparisons were made using one-way analysis of variance (ANOVA), and a p-value ≤ 0.05 was considered significant.

Results
Acute Toxicity
The results obtained are presented below.
Table 1 shows the results of the acute oral toxicity study (LD_{50} determination) in Wistar rats. The result showed behavioral changes, but no death was recorded in the rats after 24 hours and up to 14 days post-oral treatment.

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Table 3: Acute oral toxicity study (LD_{50} determination) of aqueous leaf extract of *C. odorata i*n Wistar rats

Groups	Dose(mg/kg)	Observation Period	Behavioral Changes	Mortality
Group 1 (control)n=3				
Day 1: 1st rat	D/H_20	Up to 72 hours	None	None
Day 2: 2nd rat	D/H_20	Up to 72 hours	None	None
Day 3: 3rd rat	D/H_20	Up to 72 hours	None	None
Group 2 n=3				
Day 1:1st rat	2000	Up to 72 hours	Slow movement after 2 hours of observation but becomes normal after 6 hours.	None
Day 2: 2nd rat	2000	Up to 72 hours	Same as above	None
Day 3: 3rd rat	2000	Up to 72 hours	Same as above	None
Group 3 n=3				
Day 1: 1st rat	5000	Up to 72 hours	Sluggish movement after 2 hours of observation, which deteriorates as time increases	None
Day 2: 2nd rat	5000	Up to 72 hours	Same as above	None
Day 3: 3rd rat	5000	Up to 72 hours	Same as above	None

Table 2: Hepatic Profiles in Acute Toxicity Study Wistar Rats Exposed to *C. odorata* Aqueous Leaf Extract

	Acute Toxicity Study				
Parameters	**Control**	**2000mg/Kg**	**5000mg/Kg**	**F-Value**	**P-value**
ALB (g/L)	34.67±0.88	31.33± 4.63	26.67± 3.48	71.93	0.042*
TP (g/L)	71.67±6.01	57.67± 2.33	50.00±2.89	20.88	0.032*
ALT (U/L)	9.00 ±0.58	28.33±1.76	86.33±2.03	53.621	0.000*
AST (U/L)	8.00 ± 0.58	42.00±2.31	69.00±0.58	196.65	0.021*
ALP (U/L)	55.33±3.5	81.67±6.01	76.67±14.53	81.81	0.011*
TBIL (µmol/L)	10.00±1.15	18.33±1.45	25.00±1.15	34.133	0.044*
DBIL (µmol/L)	4.67±0.88	9.00±0.58	13.67±0.88	13.07	0.038*

All measured values were presented in Mean ± SEM. n = Number of animals in the group
ALB: Albumin concentration, TP: Total Protein, ALT: Alanine Aminotransaminase, AST: Aspartate Aminotransferase, ALP: Alkaline Phosphatase, TBIL: Total Bilirubin, DBIL: Direct Bilirubin *P-value ≤ 0.05 was considered significant

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Table 3: Renal Profiles in Acute Toxicity Study Wistar Rats Exposed to *C. odorata* Aqueous Leaf Extract

	Acute Toxicity Study				
Parameters	**Control**	**2000mg/Kg**	**5000mg/Kg**	**F-Value**	**P-value**
Urea (mmol/L)	2.83 ± 0.22	4.100 ± 0.10	4.83 ± 0.17	79.524	0.002*
Creatinine(µmol/L)	70.67 ± 2.33	106.33 ± 2.60	170.33 ± 5.23	234.57	0.014*

All measured values were presented in Mean ± SEM. n = Number of animals in the group. *P-value ≤ 0.05 was considered significant

Table 4: Hepatic Profiles in Sub-Chronic Toxicity Study Wistar Rats Exposed to *C. odorata* Aqueous Leaf Extract.

	Sub-Chronic Toxicity Study					
Parameters	**Control**	**500mg/Kg**	**1000mg/Kg**	**1500mg/Kg**	**F-Value**	**P-value**
ALB (g/L)	30.20± 1.24	35.00± 1.30	41.80± 0.66	45.80± 0.86	71.93	0.012*
TP (g/L)	63.40±0.93	73.00±1.22	82.20±0.86	89.60±0.75	20.88	0.028*
ALT (U/L)	16.80±1.39	26.00±1.41	43.40±1.21	60.80±0.86	53.621	0.002*
AST (U/L)	24.20±0.86	45.40±1.33	88.80±3.10	116.40±2.34	196.65	0.010*
ALP (U/L)	37.40±1.25	82.00±2.77	99.20±0.96	122.60±3.16	81.81	0.011*
TBIL (µmol/L)	4.40±0.24	6.60±0.40	9.00±0.44	13.20±0.86	34.133	0.031*
DBIL (µmol/L)	1.60±0.2	3.00±0.45	5.80±0.37	8.00±0.32	13.07	0.046*

All measured values were presented in Mean ± SEM. n = number of animals in the group. ALB: Albumin concentration, TP: Total Protein, ALT: Alanine Aminotransaminase, AST: Aspartate Aminotransferase, ALP: Alkaline Phosphatase, TBIL: Total Bilirubin, DBIL: Direct Bilirubin *P-value ≤ 0.05 was considered significant

Table 5: Renal Profiles in Subchronic Toxicity Study Wistar Rats Exposed to *C. odorata* Aqueous Leaf Extract

	Sub-Chronic Toxicity Study					
Parameters	**Control**	**500mg/Kg**	**1000mg/Kg**	**1500mg/Kg**	**F-Value**	**P-value**
Urea (mmol/L)	3.22 ± 0.10	4.36 ± 0.10	5.40 ± 0.15	6.32 ± 0.15	79.524	0.020*
Creatinine(µmol/L)	104.20±0.97	89.40±2.23	74.40 ± 1.36	64.00 ± 1.41	234.57	0.031*

All measured values were presented in Mean ± SEM. n = Number of animals in the group *P-value ≤ 0.05 was considered significant

Discussion

Many pharmaceutical drugs and medicinal herbs can be toxic at some doses while being therapeutic at others. As traditional medicines gain popularity worldwide, the toxicity associated with them is increasingly being recognized (Bashar *et al.*, 2006). The bioactivity of *C. odorata* is believed to be attributed to its phytochemical constituents, which include pyrrolizidine alkaloids, terpenes, anthraquinones, glycosides, protease inhibitors, allicin, saponins, tannins, and sterols (Anyanwu *et al*., 2017).

Following a single dose of the 2000 mg/kg extract, an acute toxicity study revealed weight loss, pale fur, nose, and skin, incontinence, piloerection, sweating, salivation, and slow movement two hours after administration, which normalized after 6 hours; however, it was more severe with the 5000 mg/kg aqueous extract (Table 1). It shows that the LD_{50} exceeds 2000 mg/kg, implying that it is safe for human consumption at this dose but toxic at 5000 mg/kg. The Globally Harmonized System of Classification of Chemicals states that any chemical that has an LD_{50} of more than 5000 mg/kg is safe for ingestion by humans. Our findings are consistent with those of Asomugha *et al.* (2014), who reported an LD_{50} of 2154 mg/kg, implying that the aqueous extract of *C. odorata* does not have significant acute toxic effects. In addition, Van Leeuwen *et al*. (2007) suggested that chemical substances with LD_{50} > 5000 mg/kg but <5000 mg/kg are at worst slightly toxic or not significantly toxic.

The leaf's relative nontoxicity was supported by the fact that only the very high-dose groups showed adverse toxic effects. Some of the adverse toxic effects observed were: breathing irregularities, piloerection, respiratory depression, gait disturbances, and loss of spinal and pain responses. A decrease in body weight is frequently the first indicator of the onset of an

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adverse effect. The reduced growth rate observed in the highest dose group was not entirely unexpected, as the death of livestock that consumed *C. odorata* leaf has previously been reported (Asomugha *et al.,* 2014). For the subchronic toxicity study, no significant change was seen after administering various grades of the *C. odorata* extract, ranging from 500 mg/kg, 1000 mg/kg, and 1500 mg/kg.

In mammals, the liver is the primary site of xenobiotic metabolism. Several hepatotoxicants have been developed to promote tissue repair and liver cell division because these processes occur simultaneously in the body in response to injury (Calabrese & Mehendale, 1996). As the administered extract concentration increased, we observed significantly higher levels of serum liver enzyme activities and bilirubin, with a decrease in total protein and albumin concentrations. This implies that acute or chronic exposure to toxicants can cause liver injury, which can negatively impact all of the liver's primary functions, resulting in the leakage of cellular enzymes into plasma. The extent and type of such liver injury or damage can be assessed based on the level of enzyme activities in the bloodstream. Our findings are consistent with the previous studies (Yakub *et al*., 2003; Asomugha *et al.,* 2014), which also reported that administration of the extract was associated with dose-related changes in the liver: dose-related hepatomegaly, significantly elevated serum liver marker enzymes, and bilirubin, with a significant reduction in the serum total protein and albumin fraction. Elevated levels of serum ALT are an indication of hepatocellular injury. Elevated levels of AST indicate hepatitis or liver cirrhosis. Elevated levels of ALP indicate liver damage. This, however, is in contrast to Anyanwu *et al*. (2017), who reported that at the concentration of the extract they used, there were significantly decreased ($p<0.05$) activities of AST, ALT, and ALP.

Pyrrolizidine alkaloids are one of the major constituents of *C. odorata.* These are known carcinogens (Fu *et al*., 2002) and exhibit hepatotoxicity (Radominska-Pandya, 2010). They also cause hepatic veno-occlusive disease as well as liver cancer. Plants produce it to protect themselves from insect herbivores. However, other factors, such as stress and starvation, may have contributed significantly to the increase caused by increased protein metabolism. This observation aligns with the findings of Asomugha *et al*. (2014), who also observed reduced feeding rates in the rats, which may be attributed to stress.

This study observed that the rats' levels of urea and creatinine significantly increased ($p<0.05$) as the extract concentrations increased, which is consistent with previous studies (Asomugha *et al.,* 2014; Anyanwu *et al*., 2017). The significantly increased levels of creatinine and urea observed in all the groups when compared with the control ($p < 0.05$) as observed in this study, may be a result of the adverse effect of the extract on the kidneys. The pyrrolizidine alkaloids' toxic effects on the kidney could be the cause of this significant increase in creatinine and urea levels (Pfaller & Gstraunthaler, 1998; Anyanwu *et al*., 2017). The functional capacity of the kidneys' nephrons could be evaluated using creatinine and urea. Thus, the significantly altered levels ($P<0.05$) observed in this study may indicate a hepatotoxic and nephrotoxic effect of the plant extract at a higher dosage.

Conclusion

This study demonstrated that the aqueous extract of *C. odorata* significantly alters the hepatic and renal profiles, suggesting that it may adversely affect liver and kidney function, particularly at higher concentrations. Thus, the toxicological effect of the extract is dose-dependent.

Recommendation

Based on the findings of this study, *C. odorata* should be consumed with caution. Furthermore, it is recommended that further research be conducted to corroborate the findings revealed in this study and to investigate the effect of higher doses of *C. odorata.*

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Conflict of interest

None

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