Biological and Environmental Sciences Journal for the Tropics
Volume 21, Number 3, December 2024. Pp 226 - 233
https://dx.doi.org/10.4314/bestj.v21i3.21

Research article

Toxicological Effect of Aqueous n-hexane Leaf Extract of *Anacardium occidentale* on Liver and Kidney Parameters of Albino Wistar Rats

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Submission: 08/08/2024
Accepted: 29/12/2024

Abstract

Anacardium occidentale is a plant known for its vast medicinal properties and has been used in Nigeria for the treatment of several ailments. However, little is known about the toxic effects of aqueous n-hexane leaf extract on liver and kidney. The study aimed to assess the toxic effect of the aqueous N-hexane leaf extract, by examining its yield, phytochemical composition, and toxicity levels. Conducted on 27 adult albino wistar rats, the research included acute and sub-acute toxicity assessments. The extract, obtained with a yield of 18.66%, revealed the presence of alkaloids, flavonoids, steroids, phenolic compounds, and tannins, while lacking saponins. Acute toxicity tests showed no adverse effects at 5000mg/kg body weight dosage. In the sub-acute phase, rats were administered doses ranging from 100 to 400mg/kg body weight for 7 and 14 days. Body weight decreased with increased in administration. When compared with the control, organ body weight ratios for the liver and kidneys, exhibited non-significant ($p>0.05$) difference across dosage groups. Liver and kidney function parameters remained largely unaffected ($p>0.05$) when compared with the control. The findings suggest that the extract may not pose any adverse effects on liver and the kidney function at doses of 100, 250 and 400mg/kg after 14 days of administration.

Keywords: Phytochemicals, Acute toxicity, Sub-acute toxicity, Cashew leaves, Percentage yield, Organ body weight ratio

Introduction

Nigeria is blessed with potential medicinal plants, one of which is cashew plant. The cashew (*Anacardium occidentale*) is a tree in the family of the Ancardiaceae flowering plant, the family contains 73 genera and about 600 species (Oyesomi and Ajao, 2011). The plant is a medium-sized (6-9m high) spreading-evergreen tree which is widely grown in the tropics for its edible fruits and nuts. The fruit consists of a fleshy, red or yellow, pear-shaped receptacle termed the 'apple' at the distal end (Nwachukwu *et al*., 2023). The plant is popularly known in Nigeria because of its fruit, which is called "kaju" in Yoruba, "kasu" in Hausa and "kashuu" in Igbo. Cashews are repoted to be a rich sources of polyphenols and carotenoids and consumption of the nuts have been linked to benefits like weight loss, improved blood sugar control, and a healthier heart (Olatunya, 2021; Konan and Bacchi, 2007; Olatunya, 2021). Flavonoids (quercetin-3- *O*-rhamnoside, kaempferol-3-*O* methyl-ether, myricetin-3-*O*rhamnoside, kaempferol-3-*O*-rhamnoside and amentoflavone) and tannins have also been reported to be present in the Indian cashew leaf (Konan *et al*., 2006).

The nutritional benefits and medicinal values of the nut have been reported by Tola and Mazengia (2019); Zubairu *et al*. (2021); Nwosu and Onwuka (2023). The systolic blood pressure reduction and an increased HDL cholesterol concentration of cashew nut supplementation has been reported by Mohan *et al*. (2018). Different parts of this plant have also been reported by many researchers to be used for the management of diseases such as diabetes, infection, diarrhea, hemorrhage, and as antimicrobial (Silva *et al*., 2016: Ajao *et al*., 2022). Souza *et al*. (2017) and Oviosun *et al*.

(2022) reported the antioxidant and anti-inflammatory effects of *Anacardium occidentale* leaf extracts. The cashew leaf and the leaf extract enriched with zinc have been reported as a good source of antidiarrheal agents (Udedi *et al*., 2013). Leaf extract prevent lead acetate-induced liver and kidney toxicity by decreasing oxidative stress and inflammation in rats (Aminu *et al*., 2023). Research studies on the hexane leaves extract of *Anacardium occidentale* has been reported to show toxic effects at higher doses in mice (Tédong *et al*., 2007). The daily administration of aqueous extract of stem back of cashew tree have been reported to alter liver and kidney status to exhibit toxic effects at higher dose in rat (Famurewa *et al*., 2018). The aim of this study is to determine the phytochemicals present in aqueous N-hexane leave extract, lethal dose (LD_{50}) of the extract, effect of the extract on body weight, organ body weight ratio and liver and kidney parameters of albino wistar rats.

Materials and Methods

Plant Material Collection and Identification

Anacardium occidentale leaves were collected from the Botanical Garden in Nigeria Police Academy, Wudil, Kano. Plant was authenticated and deposited in the Herbarium Unit of the Department of Plant Biology, Bayero University, Kano, Kano State, Nigeria with the Voucher Specimen of BUKHAN 0296.

Extraction of Plant Materials

Preparation of *A. occidentale* leaves extract was conducted in the Department of Biochemistry and Forensic Science, Faculty of Sciences, Nigeria Police Academy, Wudil, Kano State, Nigeria. The under-shade air-dried leaves were pulverized into powder. About 500g of the powder was macerated in 3.0L of aqueous N-hexane (50% N-hexane and 50% water). After 4 days with interval shaking, the solution was filtered using Whatman No 1 filter paper and evaporated to dryness using oven at 70^{o}C. The percentage yield calculated using Equation 1:

$$\text{Yield (\%)} = \frac{Weight\ of\ the\ extract\ Gotten}{Weight\ of\ the\ Powder\ Taken}\ X\ 100 \quad \text{.....Equation 1}$$

Phytochemical screening

The methods of Gupta *et al*. (2013), Somit *et al*. (2013) and Yumnamcha *et al*. (2014), were used for detection of different phytochemicals present in the Aqueous-N-hexane extract of *A. occidentale* leaves.

Experimental Design

Acute Toxicity (LD_{50})

Acute toxicity (LD_{50}) study of the Aqueous-N-hexane extract was carried out using up and down procedure. Three albino rats with the weight of 160.4g, 176.6g and 189.4g were randomly picked and were administered 3.2ml, 3.5ml and 3.8ml of 250mg/ml of the extract respectively, the three rats were carefully observed for 24 hours, to see any signs of toxic effect at the highest dose of 5000mg/kg (OECD, 2001). The doses administered were calculated using Equation 2:

$$V(ml) = \frac{D\ X\ B}{C} \quad \text{.....Equation 2}$$

Where
V: Volume (mL)
D: Dose used (mg/kg body weight)
B: Body weight (Kg)
C: Concentration (mg/mL)

Sub-Acute Toxicity Study

Twenty-four (24) Wistar albino rats were selected by stratified randomization and then divided into four groups of six rats each and treated for 14 days as follows: Group I (Control group): received distilled water only, Group II, Group III and Group IV received 100mg/kg, 250mg/kg and 400mg/kg of extract respectively. The first day of

dosing was taken as day 0 and blood was collected on day 14 and used for biochemical analysis (Salawu *et al*., 2019).

Percentage Body Weight and Relative Organ Body Weight Ratio

The body weight of each rat was expressed using a calibrated weighing balance during the acclimatization period, once before the commencement of dosing, during the period of dosing and on the 14th day before the animals were sacrifice (Salawu *et al*., 2019). After sacrificing the animals, the liver and the kidney of each animals was removed, weight taken and compared with their body weight.

Collection of Blood

Blood samples were collected by the orbital technique. Blood sample for biochemical analysis was collected from the retrobulbar plexus of the medial canthus of the eye to enable outflow of blood into labeled centrifuge tubes, allowed to clot and centrifuged for 15 minutes at 3000 rpm to separate serum and the serum was used for biochemical analysis.

Determination of Biochemical Parameters

The analysis was carried out to determine the serum concentrations of creatinine, urea, Na^+, K^+, Cl^-, total protein, albumin, bilirubin, and activities of liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) using standard laboratory procedure.

Statistical Analysis

The data obtained were presented as the mean ± standard error of the mean (SEM). One-way analysis of variance (ANOVA), Graph pad instant software, version 26 (San Diego, USA) was used to compare means across the groups. Mean values with $p < 0.05$ were considered statistically significant.

Results

Percentage Yield

Percentage yield after the extraction of *Anacardium occidentale* leaf using Aqueous-N-hexane solvents in the ratio of 1:1 (v/v), the percentage yield for the crude extract was 18.66% (w/w) (Table 1).

Table 1: Percentage yield of Aqueous-N-hexane leaves extract of *A. occidentale*

	aqueous n-hexane leaves extract
Weight of leaves (g)	500
Weight of Extract after evaporation (g)	93.3
Percentage yield (%)	18.66

Phytochemical Results

Table 2 showing the qualitative phytochemical compounds present in Aqueous-N-hexane leaves extract of *A. occidentale*, which includes alkaloids, flavonoids, tannins, phenolic compound and steroids, while saponins are absent. In the acute toxicity of the Aqueous-N-hexane extract, the rats dosed with 5000mg/Kg body weight of the extract showed no signs of toxicity and no death was recorded after 24 and 48 hours respectively (Table 3).

Percentage Body Weight

The body weight of the rats dosed with extract for 14 days showed a decrease in weight as the concentrations increases from 7 and 14 days when compared with the control group (Table 3).

Table 2: Phytochemical present in Aqueous-N-hexane leaves extract of *A. occidentale*

Phytochemical compounds	Sign	Remarks
Alkaloids	+	Present
Flavonoids	+	Present
Saponins	-	Absent
Phenolic Compounds	+	Present
Tannins	+	Present
Steriods	+	Present

Acute Toxicity Study (LD_{50})

Table 3: Medial lethal dose (LD_{50}) of Aqueous-N-hexane leaves extract of *A. occidentale*

Dosed (mg/Kg)	Number of rats	Number of Death
5000	1	0
5000	1	0
5000	1	0

Table 4: Effect of Aqueous-N-hexane leaves extract of *A. occidentale* on body weight

Grouping (mg/Kg)	7 days Weight gain (%)	14 days Weight gain (%)
Control	5.41	9.80
100	17.33	10.26
250	-3.36	-2.73
400	-2.63	-1.69

(-) Negative percentage indicates weight loss: Weight gain was calculated using Equation……. 3

$$\% \text{ Weight gain} = \frac{Final\ weight - Initial\ weight}{Initial\ weight} X\ 100 \quad \text{.....Equation 3}$$

Relative Organ Body Weight

The effect of the extract on the relative organ body weight shown on Table 5, where the liver and the kidney showed non-significant ($p > 0.05$) difference in all the treated groups, when compared with the control group.

Table 5: Effect of Aqueous-N-hexane leaves extract of *A. occidentale* on Organ body weight ratio

Grouping (mg/Kg)	% Organ weight ratio (Liver)	% Organ weight ratio (Kidney)
Control	3.57 ± 0.45^a	0.795 ± 0.076^a
100	3.76 ± 0.21^a	0.698 ± 0.059^a
250	3.62 ± 0.40^a	0.728 ± 0.143^a
400	3.44 ± 0.54^a	0.643 ± 0.043^a

The value is presented as mean ± SEM (standard error of the mean); (n = 6), values with the same superscript as control are non-significant ($p > 0.05$) difference. The % organ body weight was calculated using Equation 4:

$$\% \text{ organ body weight} = \frac{Organ\ weight}{Body\ weight} X\ 100 \quad \text{.....Equation 4}$$

Effect of Aqueous-N-hexane Extract on Liver Function Parameters

It was observed that repeated daily oral administration of the extract at 100, 250 and 400 mg/Kg body weight for the period of 14 days did not show significant ($p > 0.05$) difference in the serum levels of AST, ALT, ALP, Bilirubin, Total protein, and albumin of the treated groups compared with the control group (Table 6).

Table 6: Effect of Aqueous-N-hexane leaves extract of *A. occidentale* on Liver Parameters

Grouping (mg/Kg)	AST (u/l)	ALT (u/l)	ALP (u/l)	Bilirubin (mg/dL)	Total protein (g/L)	Albumin (g/L)
Control	19.75 ± 0.48^a	3.50 ± 0.50^a	47.77 ± 16.12^a	1.13 ± 0.37^a	62.58 ± 2.33^a	57.98 ± 1.51^a
100	20.00 ± 0.91^a	3.33 ± 0.33^a	46.67 ± 6.54^a	1.55 ± 0.53^a	62.73 ± 1.52^a	56.05 ± 1.35^a
250	21.13 ± 0.52^a	3.50 ± 0.29^a	45.64 ± 7.78^a	1.54 ± 0.11^a	61.84 ± 1.10^a	56.73 ± 1.93^a
400	21.18 ± 0.66^a	3.75 ± 0.75^a	46.89 ± 5.69^a	1.67 ± 0.41^a	60.24 ± 4.16^a	56.03 ± 1.34^a

Values are presented as mean ± SEM (standard error of the mean); (n = 6), values with the same superscript as control are non-significant ($p > 0.05$) difference.

Effect of Aqueous-N-hexane Extract on Kidney Function Parameters

The effect of Aqueous-N-hexane leaves extract of *A. occidentale* on the serum levels of creatinine, urea, Na^+, K^+ and Cl^- are presented in Table 7. The levels of the kidney parameters (creatinine, urea, Na^+, K^+ and Cl^-) analyzed in all the treated groups show non-significant ($p > 0.05$) difference from the control.

Table 7: Effect of Aqueous-N-hexane leaves extract of *A. occidentale* on Kidney Parameters

Grouping (mg/Kg)	Sodium (Na^+) (mmol/L)	Potassium (K^+) (mmol/L)	Urea (mg/dl)	Chloride (Cl^-) (mmol/L)	Creatinine (mg/dl)
Control	114.15±16.54[a]	7.80±0.13[a]	3.38±1.02[a]	86.78±1.06[a]	13.62±1.15[a]
100	112.95 ±4.45[a]	8.18±0.91[a]	2.89±0.67[a]	87.62±0.68[a]	13.88±1.71[a]
250	114.73±7.15[a]	8.25±0.83[a]	3.18±0.45[a]	86.48±0.73[a]	14.18±2.42[a]
400	113.88±18.97[a]	7.90±0.94[a]	3.28±0.76[a]	86.60±2.56[a]	14.23±2.04[a]

Values are presented as mean ± SEM (standard error of the mean); (n = 6), values with the same superscript as control are non-significant ($p > 0.05$) difference.

Discussion

From the history of drug discovery, plants have been an important source of drugs (Konan *et al*., 2006), and this has aided the human use of herbal medicine. Humans have undoubtedly used medicinal herbs since ancient times, and this has resulted in increasing people's awareness of their properties. The presence of various physiologically active agents, namely, phytochemicals or secondary metabolites are the basis for their medicinal use (Al-Ahmad *et al.*, 2024), and different solvents were used for the extraction of these active compounds. The use of solvent in extracting the component of the plant is very important in the field of herbal medicine. In this research, aqueous N-hexane was used, and 18.66% of the extract was gotten (Table 1), which is a very good yield when compared to 8.73% and 1.83% reported for methanol and hexane by Tédong *et al*. (2007). Konan and Bacchi, (2007) reported 26.11% for ethanol leaf extract, while Onasanwo *et al*., (2012) reported 1.67%, 1.17%, 20%, and 23.3% from hexane, dichloromethane, methanol and aqueous solvents respectively. Varghese *et al*., (2013), also reported 16.9% and 12.8% (w/w) for aqueous and methanol extract.

Phytochemicals are enriched with different pharmacological activities, and these activities have a potential to be used for therapeutic purpose (Afzal *et al*., 2023). The pharmacological and toxicological activity of most herbal medicines has been linked to the presence of alkaloids, triterpenoids, flavonoids, saponins, tannins, and other compounds in the herbs (Otemenyin *et al*., 2013). The qualitative analysis of phytochemicals in the aqueous N-hexane leaves extract showed the presence of alkaloids, flavonoids, steroid, phenolic compound, and tanins, while saponins was absent (Table 2). This is in accordance with the works of Varghese *et al*., (2013), Nwosu *et al*., (2023) and Anaziah, (2023) who also reported the presence of carbohydrates, tannins, resins, alkaloids and flavonoids in cashew leaves extracts. Abulude *et al*. (2010), also reported the absence of saponins in aqueous stem extract, while its presence in aqueous leaves extract.

The acute toxicity (LD_{50}) values help in determining the safest dose to be used in the sub-acute experiments. The LD_{50} of the aqueous N-hexane extract is above 5000mg/Kg (Table 3). In the LD_{50} for this extract, no death was recorded after 24hours of administration. Observation of the animals for another 48hours showed no form of delayed toxicity and no mortality was observed, which indicated that the extract may be safe. This is in accordance with the work of Tédong *et al*. (2007), who also reported LD_{50} above 16g/Kg in mice for hexane leaves extract. 5000mg/Kg is above the safety limits given by Konan and Bacchi, (2007), where 2000mg/Kg was reported for ethanol leaf extract, while 4525mg/Kg was reported for aqueous leaf extract by Iyare *et al*., (2017) and Anaziah, (2023) also reported same value for ethanol extract. Okereke *et al*., (2020) reported the LD_{50} of cashew nut shell oil (CNSO) to be 1000mg/Kg. The part of the plants, type of solvents used and route of administrations may have aided the observed difference.

The percentage body weight gains and relative organ weight has been used as an indicator of

adverse effects of xenobiotic such as drugs and chemicals (Salawu *et al*., 2019). In this research, the percentage body weight gains were negatively affected by the extract, where there were reductions in weights of the treated rats at the doses of 250 and 400mg/Kg body weight when compared with control as the doses and duration of administration increases from days 7 to 14 (Table 4). This indicated that, the extract may have inhibited the normal growth process, or the reductions in weights may have been due to reduction in food intake (loss of appetite) or poor metabolism of the ingested food. Bioavailability of protein may be prevented by the presence of tannin in the extract (Table 2), and this can also be the cause of observed decrease in weight gain (Alagbaoso *et al*., 2015; Salawu *et al*., 2019). This result is in accordance with the work of Iyare *et al*., (2017), who have also reported the negative effects of ethanol leaves extract on the body weight of the treated rats. The relative organ weight ratio for the liver and the kidney in the treated groups showed non-significant ($p > 0.05$) difference from the control (Table 5). Ramakrishna *et al*. (2015) in Ijioma *et al*. (2018) reported that organ weight can be one of the most sensitive indicators of an effect of a test substance as significant differences in organ weights between treated and untreated (control) animals may occur in the absence of any morphological changes.

The little changes observed in relative organ weights in the treated groups may be due to the observed body weight changes. Hence any slight decline in body weight without corresponding effect on the organ weight will lower the relative organ weight values. It has been reported that minimal increase in organ weights without any microscopic lesion can be correlated with enzyme induction (Ramakrishna *et al*., 2015). Liver toxicity is measured based on activity of ALT, AST, ALP, total protein, albumin and bilirubin. An elevated level of AST, ALT, and ALP in serum have been reported as an indication of hepatocellular disruption, due to the damage to structural integrity of the liver which is deranged or compromised, leading to leakage of these enzymes from the cytosol into the bloodstream (Ighodaro and Omole, 2010; Salawu *et al*., 2019), while the bilirubin is an important metabolic product of the blood with biological and diagnostic values (Ighodaro and Omole, 2010). Total protein and albumin can be used as markers for assessing the functional capacities of the liver (Pendota *et al*., 2010). The non-significant ($p > 0.05$) difference in all these parameters in rats treated with the extract suggest that the sub-chronic administration of this extract does not seriously affect hepatocyte function in the rats or induce any serious cytotoxic damage to the liver at the tested dose.

The kidney functioning capacity was also assessed by measuring the levels of electrolytes, creatinine, and urea in the serum of the animals. The non-significant ($p > 0.05$) effect of the extract on the serum K^+, Na^+, urea, Cl^- and creatinine of the treated animals also suggest that the normal functioning of the kidney in relation to these parameters were unaffected (Table 7). This result is in contrast with the reports of Tédong *et al*. (2007) where the hexane leaves extract was reported to have an effect on the liver and kidney parameters of mice, while the work of Dave *et al*., (2020), also reported liver toxicity of methanol leaves extract of *Anacardium occidentale* in albino rats. The result is in agreement with the work of Konan *et al*., (2007) who reported that ethanol leaf extract have no toxic effect on the ALT and AST.

Conclusion

The results obtained in this study indicated that the aqueous N-hexane leaves extract of *A. occidentale* have lethal dose (LD_{50}) above 5000mg/Kg and may have no toxic effect on the liver and kidney at the doses of 100 250 and 400 mg/Kg body weight within 14 days of oral administration.

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