



EFFECTS OF ETHANOLIC EXTRACT OF *Nauclea Latifolia* STEM BARK ON LIPID PROFILE, LIVER AND KIDNEY FUNCTION IN SWISS ALBINO MICE AFTER EXPOSURE TO CRUDE OIL
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ABSTRACT

The study was carried out to investigate the effects of the administration of ethanol extract of *Nauclea latifolia* stem on lipid profile, liver, and kidney parameters of mice fed with crude oil contaminated diets (CCD). Twenty-four rats were grouped into six groups. Each group consists of four rats. Group A served as the negative control and was fed with CCD and left untreated while Group B was administered with 0.1ml of vitamin C. Groups C, D and E were administered 500, 2000 and 5000 mg/kg of ethanol extract of *Nauclea latifolia* stem, respectively while group F was administered 2 mL distilled water and fed with normal diet. Administration lasted for twenty-eight days, after which the mice were sacrificed twenty-four hours after administration on the twenty-eight day. Blood samples were collected by ocular puncture, and alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, urea, creatinine, as well as lipid profile evaluated. The results showed a significant ($p < 0.05$) concentration-dependent decrease in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG). Administration of 2000 mg/kg of the extracts significantly reduced serum urea, while the extracts had no significant effect on serum creatinine. There was a significant reduction ($p < 0.05$) in liver aspartate aminotransferase and alkaline phosphatase activities. However, the extract administration resulted in a significant increase in liver alanine aminotransferase. This revealed the lipid profile and renal function-protecting effect of the extracts. However, the ethanolic extracts at the doses administered might pose some toxicity to the liver.

Keywords: Contaminated Crude Diet, Lipid Profile, Liver, *Nauclea latifolia*, Renal Function

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INTRODUCTION

Crude oil, which is chiefly composed of hydrocarbons, some trace metals, and heavy metals (Goldstein *et al.*, 2011), has been reported to be toxic primarily due to its heavy metal content. These heavy metals, such as arsenic, mercury, cadmium, and lead, are of concern to public health because of their ability to cause major organ failure even at low exposure (Nyeche *et al.*, 2015). The exposure to some of these harmful constituents (heavy metals) of crude oil alters the normal body metabolic processes with some adverse effects on major organs and systems such as pulmonary, dermatologic, and hepatorenal systems (Ita *et al.*, 2015).

The liver and kidneys are vital in the body's metabolic processes. The liver, for instance, executes numerous functions such as metabolism, digestion, carbohydrate storage, and detoxification (Mancuso *et al.*, 2018). On the other hand, the kidneys sustain the volume of blood (homeostasis), control the level of minerals within the blood, and remove waste products of body metabolism (Reche *et al.*, 2012). It is therefore imperative to note that the major function of both the liver and the kidneys is the elimination of harmful substances. Hence, the continuous exposure to crude oil constituents could be associated with increased risk of liver and kidney dysfunction (Alqurashy *et al.*, 2023).

Nauclea latifolia (family Rubiaceae) has numerous names in Nigeria; it is called African peach in English, Ubulu inu in Igbo, tuwon biri in Hausa, and Egbesi in Yoruba (Arise *et al.*, 2012). Traditionally, different parts of the plant are used in treatment for pain, dental caries, diabetes, and diarrhoea in Africa (Gidado *et al.*, 2005). Furthermore, the plant is used as a treatment therapy for hypertension, gastrointestinal disorders, extended menstrual flow, and sleeping sickness (Elujoba, 1995).

Previous reports showed that phenolic-rich extracts of *N. latifolia* fruit improve lung tissues and haematology toxicity induced by lead acetate poisoning in Wistar rats (Busari *et al.*, 2021). Furthermore, *N. latifolia* fruit was reported to reverse lead acetate-induced liver and kidney damages and, at a higher dosage, reduce hepatic and renal injuries in Wistar rats (Busari *et al.*, 2021). The reports of Arise *et al.* (2012) revealed hepatotoxic and nephrotoxic tendencies of the aqueous extract of *Nauclea latifolia* stem. However, there is a paucity of literature on the restorative effects of the ethanolic extract of *N. latifolia* stem bark (ENLSB) on the kidney and liver function, and the lipid profile of Swiss Albino mice exposed to crude oil.

MATERIALS AND METHODS

Experimental Animals: Twenty-four mice weighing between 21g-35g were obtained from the Animal House, Nigeria Institute of Medical Research

(NIMR), Lagos State, Nigeria. The mice were fed with grower's marsh feed (a product of Top-Feeds) and water given ad libitum. Animals were housed in cages constructed of stainless steel and plastic under controlled conditions of a 12 h: 12 h light: dark cycle. The animals used in this study were maintained according to the guidelines as stated in the Guide for the Care and Use of Laboratory Animals.

Kits, chemicals, and reagents: The biochemical kits used were obtained from AGAPE Laboratories, Hombrechtikon, Switzerland. The chemicals and reagents used were obtained from Sigma-Aldrich Chemical Company, St. Louis, USA.

Plant collection: Fresh fruit and stem of *N. latifolia* were collected from the Ota area in Ado Odo, Ota local government, Ogun state, Nigeria. The plant was identified at the herbarium of the Department of Botany, University of Lagos, Nigeria by Dr. Rodoza George, and a specimen was deposited at the herbarium of the University.

Preparation of stem extracts: *Nauclea latifolia* plants were dried at room temperature for 7 days. A sample of the stem of *Nauclea latifolia* was dried and then pounded in a mortar; it was then further ground into powder and stored in an air-tight container until required.

The grounded stem bark sample (100g) was soaked in 1L of 80% ethanol and distilled water for three days. Ethanol extraction of the crushed *Nauclea latifolia* stem was performed using a Soxhlet apparatus with an electro-thermal heating mantle. The extract was dried in an oven at 55°C to remove all ethanol and then stored in the refrigerator until needed. The ethanol extract was re-extracted with cold water for use in this experiment. Residues were removed through filtration with Whatman No. 1 filter paper. The concentration of the extract was determined gravimetrically by drying a known volume and weighing the resulting residue. Throughout the experiment, the extract was kept refrigerated to maintain its stability.

Animal grouping: The Wistar albino mice were divided into six groups of four mice each and fed different concentrations of crude oil-contaminated diet (CCD), except for group 1, as shown below.

Group A: Negative Control CCD+ Distilled water

Group B: CCD+ 0.1ml/kg body weight of Vit C

Group C: Low dose of CCD + 500 mg/kg body weight of ENLSB

Group D: Medium dose of CCD + 2000 mg/kg body weight of ENLSB

Group E: High dose of CCD + 5000 mg/kg body weight of ENLSB

Group F: Positive control (0.5 ml/ Kg bw. 0.9% saline solution)

The crude oil was mixed with the diet of the mice at varying concentrations and was given to all groups except group F for twenty-eight days. The different doses of the extracts were administered to the mice in groups C, D and E daily for twenty-eight days. Similarly, vitamin C was also administered to the mice in group C daily for twenty-eight days, while the mice in group B had no treatment. The animals were weighed, euthanized by cardiac puncture on the 28th day after an overnight fast. Thereafter, blood samples were collected, liver and kidneys were also collected for further analysis.

Serum, liver, and kidney preparations: Serum was prepared by using the procedure described by Yakubu *et al* (2009). Briefly, the rats were euthanized by cervical dislocation at day 28, and the blood samples were collected by cardiac puncture from the inferior vena cava of the heart into serum sample bottles. The blood samples were allowed to clot at room temperature, and serum was obtained by centrifuging at 3000 rpm for 10 min. The liver and kidneys were collected, washed, blotted, and weighed as described by Busari *et al.* (2015).

Biochemical assays Marker enzymes and metabolites of liver and kidney damage All enzymes and metabolites of liver and kidney damage were determined by using appropriate biochemical kits (Randox and Agape commercial kits) according to the methods: sodium (Yakubu *et al.*, 2003), Potassium (Tietz *et al.*, 1994) and Chloride (Schoenfeld & Lewellan, 1964), alkaline phosphatase (Rec, 1972), alanine amino transferase and aspartate amino (Reitman & Frankel, 1957), total protein (Mu & Plummer, 2001), albumin (Doumas *et al.*, 1971), urea (Kaplan *et al.*, 1965), creatinine (Tietz *et al.*, 1994), Histology of the liver and kidney was performed using methods described by Busari *et al.* (2021).

Data analysis: The data were represented as Mean, \pm Standard error of mean of four replicates, which were analyzed using analysis of variance (ANOVA) and a Post hoc Duncan multiple comparisons test on SPSS version 22. p-value < 0.05 was considered significant.

RESULTS

The results obtained are presented in tables. Table 1 shows the result of the acute oral toxicity study (LD_{50}) of the stem extract of *N. latifolia* in albino mice. The mice had no behavioral changes, and no death was recorded in all treated groups (from group 1- group 3) after 48 hours of administration.

Table 1: Acute toxicity of ethanolic stem extract of *Nauclea latifolia* in albino mice

Groups	Dosage(mg/kg Body weight)	Survival ratio
1	500	0/4
2	2000	0/4
3	5000	0/4

Table 2 shows the effect of the various doses of the ethanolic extract of *N. latifolia* stem bark on the weight of mice fed with a crude oil-contaminated diet. The mice in the positive control group had the highest percentage weight gain (28 %) after the period of the experiment, while the negative control mice had the highest percentage weight loss (-15.84 %) after the experiment. The group administered with 5000 mg/kg of the extract had the highest percentage weight gain (14.5 %) amongst the treatment group, which compared favorably with the group treated with the standard drug (12.38 %). The group with the lowest dosage of the extract, 200 mg/kg, showed a percentage weight loss of (-7.99 %) while the group administered with 2000 mg/kg of the extract had a minimal percentage weight gain of 2.34%.

The lipid profile markers of the animals in the various groups were presented in Table 3. The administration of the extracts resulted in a significant decrease ($P < .05$) in serum cholesterol and LDL when compared with the negative control group and the group treated with the reference drug. However, serum VLDL showed no significant difference ($P > .05$) amongst all groups. The administration of 2000 and 5000 mg/kg of the extract significantly ($P < .05$) altered serum triglyceride when compared with the negative control and the group treated with the reference drug, and compared favorably with the positive control group. However, the administration of 500 mg/kg of the extract significantly ($P < .05$) alters serum triglyceride when compared to the negative and positive groups and compared favorably with the group administered the reference drug.

Table 2: Effect of ethanolic extract of *N. latifolia* stem bark on the weight of mice fed with crude oil contaminated diet

Groups	Weight before treatment	Weight at sacrifice	Weight difference	% Weight gain/loss
A	28.35 ± 1.70	23.86 ± 1.62	-4.49 ± -0.08	-15.84
B	20.20 ± 1.33	22.70 ± 1.77	2.5 ± 0.44	12.38
C	25.53 ± 1.95	23.49 ± 0.35	-2.04 ± -1.8	-7.99
D	25.63 ± 0.82	26.23 ± 1.06	0.60 ± 0.24	2.34
E	27.09 ± 1.49	31.02 ± 2.20	3.93 ± 0.71	14.5
F	25.00 ± 1.78	32.00 ± 2.50	7.00 ± 0.72	28

Values represent the Mean ± SD; Weight in (g)

Table 3: Effect of ethanolic extract of *N. latifolia* stem bark on lipid profile of mice fed with crude oil contaminated diet

Groups	HDL	Trig	Chol	LDL	VLDL
A	0.15 ± 0.03 ^b	1.07 ± 0.13 ^{bc}	4.88 ± 0.86 ^c	4.24 ± 0.83 ^c	0.20 ± 0.00 ^a
B	0.20 ± 0.01 ^b	1.69 ± 0.14 ^d	4.59 ± 0.49 ^c	3.64 ± 0.38 ^c	0.19 ± 0.06 ^a
C	0.18 ± 0.01 ^{bc}	1.40 ± 0.05 ^{cd}	2.40 ± 3.15 ^b	1.58 ± 3.12 ^b	0.31 ± 0.05 ^a
D	0.06 ± 0.01 ^a	0.68 ± 0.13 ^a	0.71 ± 0.06 ^a	0.34 ± 0.02 ^a	0.18 ± 0.10 ^a
E	0.49 ± 0.02 ^d	0.77 ± 0.12 ^{ab}	2.45 ± 1.50 ^b	1.61 ± 1.46 ^b	0.15 ± 0.02 ^a
F	0.50 ± 0.02 ^d	0.80 ± 0.15 ^{ab}	2.50 ± 1.55 ^b	1.65 ± 1.50 ^b	0.18 ± 0.04 ^a

Values represent the Mean ± SD. Values with the same alphabet in each column are not statistically significantly different ($P > .05$) from control for each of the parameters in the table. Whereas values with the different alphabet are statistically significantly different ($P < .05$) from the control group in each column for each parameter.

Serum HDL was significantly reduced ($P < .05$) upon the administration of 2000 mg/kg of the extract compared to the negative, positive groups, and the groups treated with the reference drug. However, the administration of 5000 mg/kg of the extract significantly increased ($P < .05$) serum HDL when compared to the negative control group and the reference drug, but compared favorably with the positive control group. The administration of 500 mg/kg of the extract significantly ($P < 0.05$) altered serum HDL compared to the positive control group.

Table 4: Effect of ethanolic extract of *N. latifolia* stem bark on selected liver enzymes of mice fed with crude oil contaminated diet

Groups	ALT (U/L)	AST (U/L)	ALP (U/L)
A	82.47 (± 13.15 ^a)	126.77 (± 4.68 ^d)	14.14 (± 1.95 ^b)
B	95.57 (± 1.40 ^b)	117.87 (± 9.40 ^c)	10.46 (± 0.83 ^a)
C	92.37 (± 2.19 ^b)	105.95 (± 2.65 ^b)	9.20 (± 1.59 ^a)
D	92.45 (± 3.67 ^b)	120.30 (± 4.62 ^c)	11.96 (± 4.22 ^a)
E	99.15 (± 1.15 ^c)	122.27 (± 10.20 ^c)	14.72 (± 3.19 ^b)
F	81.3 (± 5.15 ^a)	60.27 (± 1.33 ^a)	10.72 (± 3.19 ^a)

Values represent the Mean ± SD. Values with the same alphabet in each column are not statistically significantly different ($P > .05$) from control for each of the parameters in the table. Whereas values with the different alphabet are statistically significantly different ($P < .05$) from the control group in each column for each parameter.

Table 4 revealed the impact of the extracts on serum ALT, AST, and ALP. Administration of 500, 2000, and 5000 mg/kg of the extract did not significantly alter serum ALT compared to the positive control and reference drug. However, the three doses significantly increased serum ALT compared to the negative control group. Furthermore, the administration of both 2000 and 5000 mg/kg of the extract did not significantly alter serum AST compared to the negative, positive controls, and the reference drug, while the administration of 500 mg/kg of the extract significantly reduced serum AST activities. 5000 mg/kg of the extracts significantly increased serum ALP compared to the positive control and reference drug while administration of 500 and 2000 mg/kg of the extract did not significantly alter serum ALP when compared to the positive control and reference drug. The administration of the extract did not significantly alter serum creatinine level. However, the administration of 2000 mg/kg significantly reduced serum urea level compared to the negative control group Table 5.

DISCUSSION

Toxicity of chemicals and medicinal plants are frequently studied with animal models because of their usefulness in early identification of undesirable effect (Nurul et al., 2018). It is also well established that mortality is used to determine the acute toxicity of plants extracts and other chemicals. In addition to mortality, behavioural changes, changes in organs and

Table 5: Effect of ethanolic extract of *N. latifolia* stem bark on selected renal markers of mice fed with crude oil contaminated diet

Group	Creatinine (mmol/L)	Urea (mmol/L)
A	1.95 ± 0.00 ^a	9.48 ± 1.34 ^b
B	1.96 ± 0.03 ^a	8.04 ± 0.18 ^a
C	2.37 ± 0.29 ^a	8.70 ± 0.68 ^b
D	2.41 ± 0.25 ^a	6.68 ± 0.49 ^a
E	2.16 ± 0.19 ^a	8.71 ± 0.37 ^b
F	4.00 ± 4.50 ^b	10.30 ± 0.41 ^c

Values represent the Mean ± SD. Values with the same alphabet in each column are not statistically significantly different ($P > .05$) from control for each of the parameters in the table. Whereas values with the different alphabet are statistically significantly different ($P < .05$) from the control group in each column for each parameter.

body weight are also essential when investigating toxicity using animal models. At the acute toxicity phase, the results revealed no behavioral changes, and no death recorded in all treated group (from group 1 – group 3) after 48 hours of administration with ethanol extract of *Nauclea latifolia*. This, therefore, indicates that the ethanol stem extract of *Nauclea latifolia* may not be toxic at doses not greater than 5000mg/kg (Asare et al., 2012).

Low density lipoprotein cholesterol is often designated as “bad” cholesterol since high levels of it in the plasma are linked with increased deposition of cholesterol in the arterial walls while HDL serve as acceptors of cholesterol from various tissues. They promote the removal of cholesterol from cells and its secretion into the bile by the liver (Trajkovska & Topuzovska, 2017). The best single indicator of the likelihood of developing atherosclerotic heart disease is not total plasma cholesterol but rather the ratio of plasma LDL cholesterol to plasma HDL cholesterol. The reduction in serum total cholesterol and LDL concentration following the repeated and prolonged administration of the extract agrees with the report of Aprioku and Obianime (2009). This will normally suggest a beneficial effect in pathological conditions. The observe decreased in triglyceride following administration of the extract could be due to increase in lipolysis caused by the extract. A decrease in triglyceride that is accompanied by a decrease in LDL is associated with a decreased risk in cardiovascular events. Low density lipoprotein transport cholesterol from its site of synthesis in the liver to the various to the various tissues and body cells where it is separated and used by the cells. HDLs on the other hand, transport excess or unused cholesterol from the tissues back to the liver, where it is broken down to bile acids and then excreted.

This makes HDL beneficial to health. The significant reduction in HDL concentration, therefore, may negatively impact the function of the liver.

Liver function parameters used to detect the presence of liver disease or potential harm to the liver include the serum levels of the enzymes AST, ALT, and Alanine phosphatase. Usually, any kind of liver injury can cause a rise in ALT (Shivary et al., 2009) and the release of ALT and AST from the cytosol occurs when there is injury to hepatocytes, especially in membrane damage (Chikwendu et al., 2015). The significant decrease in liver alkaline phosphatase activity of the groups treated with 500 and 2000 mg/kg of the extract is suggestive of possible damage to the tissue cell plasma membrane. This may imply loss of the enzyme to extracellular fluids or the inactivation of the enzyme *in situ* by the components of the extract and their metabolites.

Alanine aminotransferase (ALT) activities in the blood are increased in conditions in which cells are damaged or dead. Elevation of alanine aminotransferase and aspartate aminotransferase (ALT and AST) activities in the liver homogenate following twenty-eight days of administration may indicate derangement of hepatic cytosolic content and interference with kidney amino acid metabolism. The elevation in AST and ALT in liver tissues or liver homogenate at the high doses of 2000 and 5000 mg/kg of the extract could imply some forms of inflammation of liver. Possibly, the doses of the extracts administered or the duration of administration are toxic to hepatic cells. Our findings corresponded with the reports of Ogenyi et al. (2015), who reported the increase in serum AST and ALT of rabbits exposed to ethanolic extracts of *N. latifolia*. However, our findings negate the report of Arise et al. (2012), who reported a decrease in serum AST and ALT of rats after the administration of aqueous extract of *N. latifolia* stem. Therefore, the ethanolic extracts of *N. latifolia* stem may not be beneficial in protecting the liver from crude oil contamination-induced liver anomaly.

The kidney plays a very important role in the removal of metabolic wastes from the bloodstream. Its functionality, therefore, can be assessed among many others by determining the serum concentration of excretory constituents (Spencer et al., 2011). The extracts at the doses administered showed a slight increase in the creatinine level measured, although not significant. The increased levels of blood urea in the crude oil contaminated diet group imply the inability of the kidneys to excrete this by-product, leading to their elevated levels in the blood and decreased excretion in urine (Akinrinde et al., 2020). The decrease in the urea concentration after the administration of 2000 mg/kg

of the extract resonates with the report of Busari et al. (2021), who revealed the decrease in serum urea by *N. latifolia* extracts after lead acetate-induced increase. This could be indicative of a protective effect on some kidney functions.

CONCLUSION

In conclusion, this study indicates that the ethanol stem extract of *Nauclea latifolia* may be useful in ameliorating crude oil contamination-induced lipid profile anomaly and renal function. However, the extracts showed some toxicity to the liver, which could be due to the high dosages or the length of administration.

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