Trop J Nat Prod Res, January 2023; 7(1):2258-2263 ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Chronic Administration of Hydroalcoholic Extract of *Newbouldia laevis* Leaves Induces Electrolyte Imbalance and Dyslipidemia in Wistar Rats

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ARTICLE INFO

Article history:
Received 26 December 2022
Revised 20 January 2023
Accepted 28 January 2023
Published online 01 February 2023

ABSTRACT

Newbouldia laevis is a medicinal plant widely used for various ailments in Africa,but little is known about its effect on serum electrolytes and lipids after chronic use. In this study, effects of prolonged administration of hydroalcoholic extract of *Newbouldia laevis* leaves (CEE) on serum electrolytes and lipids were investigated in rats. Wistar rats were treated daily with CEE (150 – 600 mg/kg b.w) for 120 days. Thereafter they were sacrificed and serum lipids and electrolytes were analyzed. Data obtained were analyzed by one-way analysis of variance (ANOVA) and Tukey's post hoc test, and $p<0.05$ was considered significant. The results showed that 600 mg/kg b.w of CEE caused a significant ($p<0.05$) decrease in serum levels of sodium and chloride ions. There was significant ($p<0.05$) increase in serum levels of potassium and bicarbonate ions. CEE (300 and 600 mg/kg b.w.) caused significant increase ($p<0.05$) in the serum levels of triglycerides, total cholesterol, low density lipoprotein cholesterol, and very low density lipoprotein cholesterol in the CEE-treated rats compared to the control. There was also a significant reduction in the level of high density lipoprotein cholesterol (HDL-c). Levels of these parameters were not significantly different ($p>0.05$) from the control following the 28-day withdrawal of CEE. From our findings, we conclude that prolonged use of extract of *Newbouldia laevis* leaves could result in electrolyte imbalance and dyslipidemia. Although withdrawal of the extract after long term use could ameliorate its adverse effects, the plant should be used with caution.

***Keywords*:** *Newbouldia laevis*, electrolytes, lipids, medicinal plant, chronic use

Introduction

Electrolytes are electrically charged minerals that are essential for normal cellular functions. They are found in extracellular and intracellular body compartments. The body must maintain levels of these ions within acceptable limits. Serious critical conditions and even death can occur when concentrations fall short of or surpass these limits.[1] Disturbances of specific ion balance occur frequently and for many reasons. Dietary factors and drugs often contribute to electrolyte imbalance. Sometimes, electrolyte imbalance may occur even when fluid balance is maintained. For instance, water lost when a diuretic is used can be replaced by adequate water intake, but potassium lost by diuresis is not replaced by subsequent consumption of water. This results in electrolyte imbalance that requires potassium replacement for normal cellular function.[2]

Apart from potassium, other electrolytes that are essential for normal body function include bicarbonate, chloride, sodium, and other ions.[3] Bicarbonate ion (HCO_3^-) is essential for proper acid-base balance.

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Citation: Kolawole OT, Adeyeba OA, Awodele O, Ayankunle AA, Wakeel OK, Ayelagbe OG. Chronic Administration of Hydroalcoholic Extract of *Newbouldia laevis* Leaves Induces Electrolyte Imbalance and Dyslipidemia in Wistar Rats. Trop J Nat Prod Res. 2023; 7(1):2258-2263. http://www.doi.org/10.26538/tjnpr/v7i1.26.

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In diseased conditions which trigger metabolic acidosis, such as renal disease, severe diarrhea, cardiac arrest, and diabetic acidosis, bicarbonate is administered intravenously as sodium bicarbonate ($NaHCO_3$), and orally as urinary or gastric alkalinizer to correct the deficiency of the ion.[4]

Potassium (K^+) is essential for impulse transmission, muscle contraction, and other vital physiologic processes. It is prescribed in hypokalemia caused by diabetic acidosis, severe diarrhea and vomiting, malnutrition, and other pathologic conditions that promote loss of potassium.[5]

Sodium (Na^+) is another electrolyte which plays a vital role in maintenance of normal cardiac function and regulation of osmotic pressure within the body. Administration of sodium is essential when hyponatremia results from severe vomiting and diarrhea, excessive diaphoresis, severe diuresis, and other pathologic problems.[6] Chloride (Cl^-) is the major anion in the extracellular fluid, and changes in its concentration typically mirror sodium concentrations.[7] Sodium is usually administered intravenously as normal saline (0.9% NaCl). It is also marketed as combination of 0.9% sodium chloride and 5% dextrose.

The class of substances called lipids is another group of important cellular components. This class consists mainly of fatty acids, esters of fatty acids with glycerol (monoglycerides, diglycerides, and triglycerides), phospholipids, cholesterol and other steroids. In addition, lipids can combine with proteins to form lipoproteins.[8] Dietary fat is composed mostly of triglycerides. Lipids can be absorbed in a less fully digested state than proteins and carbohydrates, but they must be emulsified by bile salts before absorption can take place. Once absorbed, lipids are transported through the lymph ducts

and blood vessels by combining with proteins to form lipoprotein complexes.[9] Some lipoproteins function as carriers for exogenous lipids from the intestine to fat cells, muscle cells, and the liver. Others are carriers for endogenous lipids, providing transport for lipids mobilized from the liver or promoting clearance and elimination. Hyperlipidemia disorders, in which levels of triglycerides or cholesterol are elevated, are secondary to abnormally high quantities of liporpoteins – a condition known as hyperlipoproteinemia.[10] High density lipoprotein, low density lipoprotein, and very low density lipoprotein are among the classes of lipoprotein that have been identified. Sustained elevation of triglycerides and low density lipoprotein cholesterol levels ultimately results in serious health issues. Such derangement in lipid levels may be precipitated by some food, drugs, and some other exogenous substances.[11,12] As stated earlier, electrolyte levels can also be altered by these substances. Therefore determining how substances we consume repeatedly as food or drug affect body lipids and electrolytes is important. In recent years, the use of alternative medicines, including herbal remedies has gained popularity. Herbal preparations are frequently taken without regard for possible adverse effects on the levels of electrolytes and lipids. This has led to many health problems among users of herbal preparations, especially in developing nations. To prevent fatalities and reduce the cost of medical care among users, it is necessary to evaluate the potentials of medicinal plants to cause electrolyte imbalance and dyslipidemia.

Newbouldia laevis is a plant widely used in some African countries as herbal remedy. It is used repeatedly to treat convulsions, diabetes and infertility.[13] Despite its widespread use, reports on its long term effects on body lipids and electrolytes are scarce. This study was carried out to evaluate the long term effects of *Newbouldia laevis* on serum lipids and electrolytes in rats.

Materials and Methods

Preparation of Plant Extract

Leaves of *Newbouldia laevis* were collected in November 2020 from Stadium area in Ogbomoso, Nigeria. The plant samples were identified at Forest Research Institute of Nigeria (FRIN) where voucher specimen (FHI 107753) was deposited. Dry samples of the plant were reduced to the powdery form by a grinding machine. The pulverized sample was extracted in 80% ethanol by a Soxhlet apparatus. A rotary evaporator (Heidolph-Rotacool, Germany) was used to concentrate the extract at 40 ºC. The extract (CEE) was kept in a refrigerator. CEE was reconstituted in distilled water during the study.

Ethical consideration

The Protocols and procedures employed in the study were as outlined in the "Guide for the Care and Use of Laboratory Animals" published by the National Research Council.[14]The study was also approved by the Laboratory Animal Use Committee of Pharmacology Department, Ladoke Akintola University of Technology, Nigeria (Number: PT21/004).

Study procedure

Male Wistar rats (8-10 weeks old, weighing 120 ± 20 g) were obtained from the Animal Holding Unit of the Department of Pharmacology and Therapeutics, Ladoke Akintola University of Technology (LAUTECH). The rats were kept in cages in a well-ventilated room. They were fed with standard commercial pellet diet and potable tap water *ad libitum.* Twelve rats were assigned to each of four major groups (I, II, III, and IV). Each group was subdivided into two as IA and IB, IIA and IIB, IIIA and IIIB, IVA and IVB. Each subgroup consists of 6 rats. The rats were orally treated daily for 120 days as follows:

IA and IB: 150 mg/kg b.w. CEE; IIA and IIB: 300 mg/kg b.w. CEE; IIIA and IIIB: 600 mg/kg b.w. CEE; IVA and IVB: 10 ml/kg b.w. distilled water. Animals in the subgroups IA, IIA, IIIA, and IVA were sacrificed after the 120-day treatment, while rats in subgroups IB, IIB, IIIB, and IVB were left for 28 days after the treatment before they were sacrificed (reversibility study).

Analysis of lipids and electrolytes

Blood samples were collected from sacrificed rats for biochemical analyses. Total cholesterol (TC), triglycerides (TG),high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) were analyzed by Automated Clinical System (Sychron Clinical System®, model: CX5 PRO; Beckman Coulter Inc., Galway, Ireland).[15-19] Very low density lipoprotein cholesterol (VLDL-C) was calculated by the formula: $VLDL = 0.2 \times TG$.[20]Serum electrolytes (sodium, potassium, chloride, bicarbonate) were analyzed by Humalyte Plus, an automated electrolyte analyzer (Human Diagnostics Worldwide).[21]

Phytochemical screening

Tests were carried out on CEE using standard procedures to identify its phytoconstituents and determine their quantity. The extract was screened for alkaloids, flavonoids, tannins, terpenoids, saponin, phenolics and cardiac glycosides.[22, 23]

Statistical Analysis

Data obtained were expressed as mean ± standard error of mean (SEM). Data were subjected to one-way analysis of variance (ANOVA) followed by Tukey's *Post Hoc* test. A level of $p< 0.05$ was taken as significant.

Results and Discussion

Treatment of rats with hydroalcoholic extract of *Newbouldia laevis* for 120 days caused a significant ($p<0.05$) reduction in serum level of sodium (Figure 1). Sodium is essential for many physiological functions including blood pressure regulation, body fluid maintenance and normal function of the nervous system.[24] A significant decrease in the level of sodium (hyponatremia), such as observed with long term use of CEE in this study, can be attributed to direct sodium depletion by the extract. It may also result from many other causes including kidney damage, heart failure, and liver cirrhosis.[25]

The mortality of patients with hyponatremia is approximately double that of patients with normal plasma sodium concentrations. It is also the most common electrolyte disorder seen in hospitalized patients.[26] Excess sodium retention and associated edema is a leading cause of hypertension, which in turn, is a major factor in overall mortality rate, especially cardiac disorders. Hypertensive patients are typically placed on sodium-restricted diets along with other therapeutic measures.[27]

Significant ($p<0.05$) increase in the serum level of potassium was observed at 600 mg/kg b.w. compared with the control after administering the extract for 120 days (Figure 2). In the reversibility studies, potassium level was significantly higher compared to the control following the withdrawal of CEE. Serum level of chloride ions was significantly ($p<0.05$) reduced at 600 mg/kg b.w. (Figure 3).

Serum level of bicarbonate ions was also significantly raised in rats treated with 600 mg/kg b.w. of CEE when compared with rats treated with distilled water as shown in Figure 4. This change was not significantly reversed after the withdrawal of CEE for 28 days. Chloride is the major extracellular anion. It is filtered and reabsorbed in the renal tubule, but for the most part, its rate of excretion varies passively in relation to other anions. It is the companion ion for excretion with various cations (Na^+, K^+, and H^+) to the extent that other anions are unavailable.[28] Chloride levels are elevated in respiratory alkalosis and sometimes in metabolic acidosis, while the levels decline in respiratory acidosis and metabolic alkalosis.[29]

Potassium is the cation in highest concentration in the intracellular fluid. It is essential for intracellular osmolality, electrical excitability of nerve and muscle cells, secretory activity, and renal function. It is also a cofactor in several enzymatic reactions of carbohydrate metabolism.[30] When serum potassium is raised significantly as observed with prolonged use of CEE, it could be due to impaired potassium excretion resulting from renal damage.[31] It may also be due to the release of intracellular potassium caused by trauma, inflammation or injury.[32] Drugs such as potassium-sparing diuretics can also cause hyperkalemia.

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

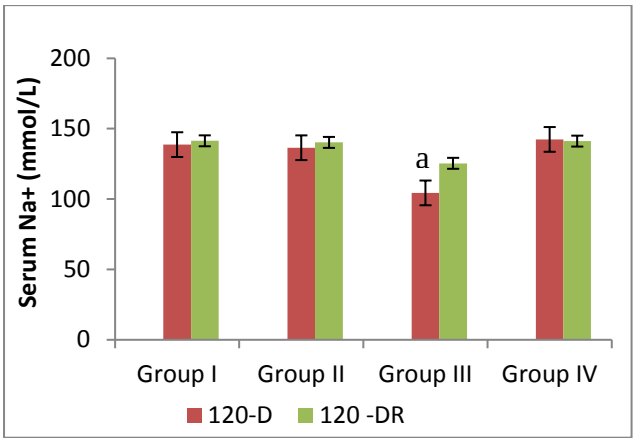

Figure 1: Effects of repeated administration of hydroalcoholic extract of *Newbouldia laevis* (CEE) on serum level of sodium ion
Group I = 150 mg/Kg b.w; Group II = 300 mg/Kg b.w; Group III = 600 mg/Kg b.w; Group IV = 10 ml/kg distilled water (n = 6);$^{a}p<0.05$ compared with control. 120-D = group of rats treated with CEE for 120 days; 120-DR = group of rats for reversibility study after treatment with CEE for 120 days

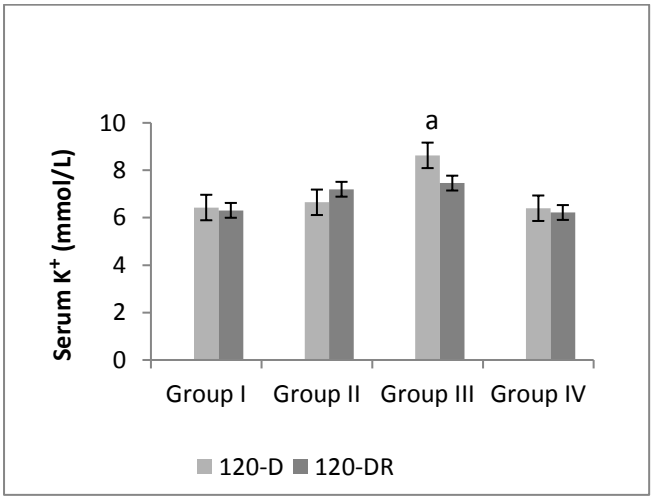

Figure 2: Effects of repeated administration of hydroalcoholic extract of *Newbouldia laevis* (CEE) on serum level of potassium ion
Group I = 150 mg/kg b.w; Group II = 300 mg/kg b.w; Group III = 600 mg/kg b.w; Group IV = 10 ml/kg distilled water (n = 6);$^{a}p<0.05$ compared with control. 120-D = group of rats treated with CEE for 120 days; 120-DR = group of rats for reversibility study after treatment with CEE for 120 days

Symptoms of hyperkalemia include muscle weakness, paresthesias, and paralysis. Bradycardia and hypotension occur at high serum level, and ventricular fibrillation and cardiac arrest at higher levels.[33] Hypokalemia is most commonly due to loss of potassium-rich gastrointestinal secretions as a result of vomiting, diarrhea, malabsorption, or use of drugs such as laxatives.[34] Extracellular potassium depletion can also be the result of transfer of potassium into the intracellular compartment, as in acute alkalosis.[35] The symptoms of hypokalemia relate to impairment of potassium-mediated functions. Muscles become weak or even paralyzed. Respiratory hypoventilation or even paralysis may occur, as well as hypotension, tetany, and twitches. Smooth muscle dysfunction occurs in the form of paralytic ileus. Cardiac manifestations include dysrhythmias and increased sensitivity to digitalis glycosides.

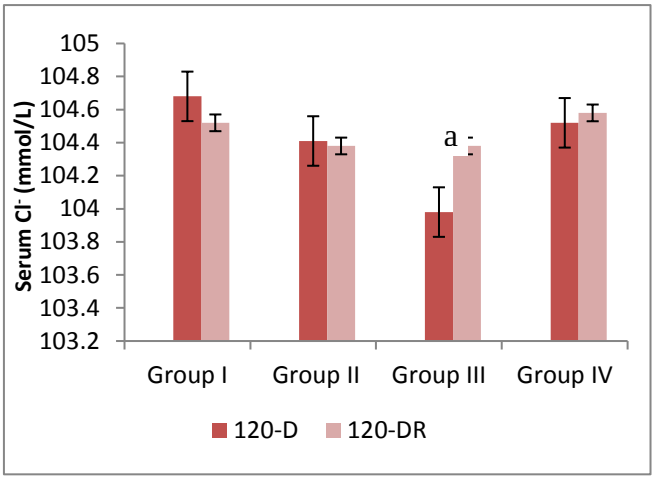

Figure 3: Effects of repeated administration of hydroalcoholic extract of *Newbouldia laevis* (CEE) on serum level of chloride ion
Group I = 150 mg/kg b.w; Group II = 300 mg/kg b.w; Group III = 600 mg/kg b.w; Group IV = 10 ml/kg distilled water (n = 6);$^{a}p<0.05$ compared with control. 120-D = group of rats treated with CEE for 120 days; 120-DR = group of rats for reversibility study after treatment with CEE for 120 days

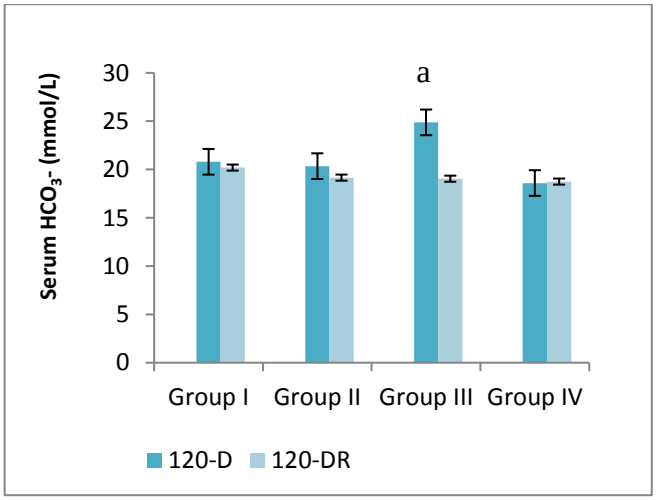

Figure 4: Effects of repeated administration of hydroalcoholic extract of *Newbouldia laevis* (CEE) on serum level of bicarbonate ion
Group I = 150 mg/kg b.w; Group II = 300 mg/kg b.w; Group III = 600 mg/kg b.w; Group IV = 10 ml/kg distilled water (n = 6);$^{a}p<0.05$ compared with control. 120-D = group of rats treated with CEE for 120 days; 120-DR = group of rats for reversibility study after treatment with CEE for 120 days

Repeated administration of 300 and 600 mg/kg b.w. CEE for 120 days caused significant increase ($p<0.05$) in the serum levels of triglycerides, total cholesterol, low density lipoprotein cholesterol, and very low density lipoprotein cholesterol in treated rats compared to the control group. There was also a significant reduction in the level of high density lipoprotein cholesterol (HDL-c) in the rats treated with CEE compared with control (Table 1). Levels of these parameters were not significantly different ($p>0.05$) from the control following the withdrawal of CEE for 28 days as shown in Tables 2.
Serum levels of triglycerides and cholesterol are important predictors of health status. Cholesterol is more a focus of concern than the triglycerides because of its relationship to atherosclerosis, high blood pressure, dementia, angina, and xanthomas. Serum levels of LDL correlate strongly with atherosclerosis and the attendant risk of life-

threatening cardiovascular diseases, including coronary artery disease, myocardial infarction, chronic organic brain syndrome, cerebral vascular accidents, thrombosis and embolism, and other thromboembolic disorders.[36]

HDL functions independently of the other lipoproteins. It originates in the liver and intestines, binds cholesterol preferentially and triglycerides secondarily, and facilitates the clearance and degradation of these lipids by the liver. In sharp contrast to LDL, the levels of HDL correlate inversely with risk of atherosclerosis.[37] Elevated levels of triglycerides may also lead to pancreatitis, eruptive xanthomas, hepatosplenomegaly, lipemia retinalis, hyperuricemia, and glucose intolerance.[38]

Significant changes in the level of serum electrolytes, total cholesterol, high density lipoprotein, low density lipoprotein, very low density lipoprotein, and triglycerides in the treated rats suggest that CEE has the potential to cause electrolyte imbalance and dyslipidemia.

Phytochemical analyses showed that *Newbouldia laevis* leaves contained tannins (31.52% w/w), saponins (10.72% w/w), flavonoids (25.82 % w/w), terpenoids (18.16% w/w) and phenolics (49.14% w/w). Cardiac glycosides and alkaloids were not detected (Table 3). These phytoconstituents present in the leaves of *N. laevis* are likely responsible for changes observed in the levels of lipids and electrolytes. High concentration of tannins has been reported to cause cancer and liver damage.[39] Since the liver is the organ responsible for metabolic processes, any exogenous substance that disrupts its normal function will also affect lipid metabolism, resulting in dyslipidemia as observed with CEE.[40] Studies have also shown that long term consumption of tannins can impair iron bioavailability. Iron is an integral part of many enzymes and transporters that play essential roles in lipid metabolism. Therefore, any substance that affects iron bioavailability will ultimately affect lipid metabolism.[41,42] Like the tannins, some terpenoids are also cytotoxic, especially when consumed in large quantity or for a long period.[43] Terpenoids present in the leaves of *N. laevis* may have also contributed to the imbalance in lipid and electrolytes in the treated rats. Phenolic compounds have likewise been demonstrated to be toxic to human when they accumulate in the body. Some of their harmful effects are kidney, heart, and liver damage.[44,45] Thus, repeated ingestion of these compounds can impact negatively on lipid metabolism and electrolyte balance.

Table 1: Lipid profile in rats treated with hydroalcoholic extract of *Newbouldia laevis* (CEE) for 120 days

Group	I	II	III	IV
Triglyceride (mmol/L)	1.62 ± 0.43*	1.56 ± 0.11*	1.93 ± 0.62*	0.79 ± 0.07
Total Cholesterol (mmol/L)	1.66 ± 0.52	2.08 ± 0.57	8.22 ± 0.85*	2.40 ± 0.13
LDL-C (mmol/L)	2.51 ± 1.43	3.74 ± 1.21*	5.93 ± 0.62*	1.85 ± 0.06
VLDL-C (mmol/L)	0.33 ± 0.08*	0.31 ± 0.02*	0.39 ± 0.12*	0.16 ± 0.01
HDL-C (mmol/L)	0.75 ± 3.33*	0.80 ± 0.17*	0.42 ± 0.11*	1.53 ± 0.25

Group I = 150 mg/kg b.w; Group II = 300 mg/kg b.w; Group III = 600 mg/kg b.w; Group IV = 10 ml/kg distilled water. Each value represents mean ± SEM (n = 6); *p<0.05 compared with control

Table 2: Lipid profile in rats treated with hydroalcoholic extract of *Newbouldia laevis* (CEE) for 120 days (Reversibility study)

Group	I	II	III	IV
Triglyceride (mmol/L)	0.71 ± 0.20	0.60 ± 0.22	0.91 ± 0.42	0.86 ± 0.11
Total Cholesterol (mmol/L)	2.61 ± 0.81	2.66 ± 0.46	2.41 ± 0.45	2.93 ± 0.10
LDL-C (mmol/L)	1.82 ± 0.30	1.64 ± 0.50	1.90 ± 0.33	1.52 ± 0.13
VLDL-C (mmol/L)	0.14 ± 0.01	0.12 ± 0.04	0.18 ± 0.08	0.17 ± 0.02
HDL-C (mmol/L)	1.50 ± 0.72	1.40 ± 0.51	1.28 ± 0.16	1.53 ± 0.25

Group I = 150 mg/kg b.w; Group II = 300 mg/kg b.w; Group III = 600 mg/kg b.w; Group IV = 10 ml/kg distilled water. Each value represents mean ± SEM (n = 6)

Table 3: Secondary metabolites in the leaves of *Newbouldia laevis*

Secondary metabolites		Result	Quantity (%w/w)
Alkaloids	Dragendorff	Negative	-
	Mayer	Negative	-
	Wagner	Negative	-
Flavonoids	Shinoda	Positive	
	Lead acetate	Positive	25.82
	Ammonia	Positive	
Saponin	Frothing	Positive	10.72
Tannin	Prussian blue	Positive	31.52
Total phenolics	Ferric chloride	Positive	49.14
Cardiac glycosides	Keller-Killani	Negative	-
Terpenoids		Positive	18.16

Conclusion

From the results, we conclude that prolonged use of hydroalcoholic extract of *Newbouldia laevis* could result in electrolyte imbalance and dyslipidemia. Withdrawal of the extract after long term use could ameliorate its adverse effects on serum lipids and electrolytes. Caution should be exercised when leaves of *N. laevis* are prepared and consumed as herbal remedy.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgements

The authors acknowledge and appreciate the logistic support provided by Mrs Cherish Kolawole, and the technical assistance by Mr I.O. Olaniran.

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