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Cardioprotective Effect of Leaf and Root Extracts of *Newbouldia laevis* against Carbon Tetrachloride Induced-Cardiotoxicity in Albino Rats

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Authors' contributions

This work was carried out in collaboration between all authors. Authors KNA, CE and EIA designed the study. Authors KNA, IKO and AJU performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MEO, NE and OPCU managed the analyses of the study and the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Various parts of *Newbouldia laevis* are used by traditional medicine practitioners in Eastern Nigeria for treatment/management of several disorders, including cardiovascular diseases. This study was designed to investigate cardioprotective potential of aqueous leaf and root extracts of the plant in albino rats. Forty-four (44) adult male albino rats, used in this study, were placed into eleven (11) groups (A, B, C, D, E, F, G, H, I, J and K), four rats in each group. Groups A, B, C and D were orally administered with 200, 400, 600 and 800 mg/kg body of leaf extract respectively, while

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groups E, F, G and H were given the same doses of root extract correspondingly. Group I received 1.2 mg/kg body weight of aspirin (a cardioprotective drug), while groups J and K were given distilled water. Administration lasted seven (7) consecutive days. On the seventh day, all groups, except K, were given 2.5 ml/kg body weight of carbon tetrachloride (CCl4) intraperitoneally two hours after extract/aspirin administration. Group K received olive oil. Phytochemical screening revealed the presence of alkaloids, tannins, saponins, flavonoids, anthraquinones, terpenoids and cardiac glycosides in the extracts. The activity of creatine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST) and concentration of cardiac troponin I (CTnI) in the serum of extract- and aspirin-treated groups were significantly lower ($P < 0.05$) than the untreated negative control in which these parameters were significantly higher ($P < 0.05$) than in normal control. Serum lipid profile of the animals also followed the same trend. There was a significant decrease ($P < 0.05$) in the concentration of malondialdehyde (MDA) in the extract- and aspirin-treated groups relative to the negative control. The activity of the antioxidant enzymes, superoxide dismutase (SOD), catalase (CAT) and glutathione reductase (GR) was significantly higher ($P < 0.05$) in the extract- and aspirin-treated groups and normal control than in the untreated negative control. The effect of the extracts were dose-dependent, and that of 800 mg/kg leaf extract was significantly higher ($P<0.05$) than 1.2 mg/kg aspirin. There was a significant difference ($P<0.05$) between the groups given leaf extract and those treated with root extract. These findings are indicative of possible cardioprotective potential of the extracts, and may be partly responsible for their efficacy against cardiovascular diseases.

Keywords: Albino rats; carbon tetrachloride; Newbouldia laevis; myocardial infarction; antioxidant activity; lipid profile; water and ethylacetate extract.

1. INTRODUCTION

Plants are used medicinally in different countries and are a source of many potent and powerful drugs. The plant chemicals are classified as primary or secondary metabolites. Primary metabolites are widely distributed in nature, occurring in one form or another in virtually all organisms. Plants generally produce many secondary metabolites which are biosynthetically derived from primary metabolites and constitute an important source of microbicides, pesticides and many pharmaceutical drugs. From a long period of time medicinal plants or their secondary metabolites have been directly or indirectly playing an important role in the human society to combat diseases [1].

Newbouldia laevis a medium sized angiosperm in the *Bignoniaceae* family. It is native to tropical Africa and grows to a height of about 10 m with a cauliferous habit. It is ever green, though its leaves turn somewhat dark purple during the cold seasons. It is popularly known as the tree of life or fertility tree in Nigeria. The root and leaves are used in the treatment of diseases such as convulsion, epilepsy, manic and cardiovascular disorders [2].

Antioxidant compounds are present high content in plants [3]. It has shown protective effects against diseases without reducing their therapeutic efficacy. Moreover, there is a growing interest in the usage of natural antioxidants as a protective strategy against cardiovascular related problems such as ischemia reperfusion [3].

Carbon tetrachloride (CCl_4) is a well-known model compound for producing chemical tissue toxicity by generation of free radicals in many tissues such as liver, kidneys, heart, lung, testis, brain and blood [4]. It is biotransformed by hepatic microsomal cytochrome P450 to trichloromethyl-free radical [5], which in turn, initiate lipid peroxidation process [6]. The most widely accepted mechanism of CCl_4 induced cardiotoxicity is the formation of free radicals which is a rate limiting process in tissue peroxidative damage [7]. This free radical and related reactive species may cause oxidative stress, which produces major interrelated rearrangements of cellular metabolism, increase in intracellular free calcium, damage to membrane ion transport and permeability, and destruction of thecells by lipid peroxidation [8]. This leads to loss of myocardial structural integrity and depressed cardiac function resulting in cardiotoxicity and congestive cardiac failure [7]. Antioxidant systems minimize or prevent deleterious effects of the ROS [9]. There is scarce documented evidence on the various medicinal applications of *Newbouldia laevis* in this part of the world. The study investigated the cardioprotective effect of leaf and root extracts of

Newbouldia laevis against CCl_4 –induced cardiotoxicity.

2. MATERIALS AND METHODS

2.1 Collection of Leaves and Roots of *Newbouldia laevis*

Fresh leaves and roots of *Newbouldia laevis* were collected in the month of October, 2014 from Izzi in Abakaliki Local Government of Ebonyi State. The samples were identified by Prof. S. C. Onyekwelu of Applied Biology Department, Ebonyi State University, Abakaliki.

2.2 Preparation of Extracts

The samples were washed with distilled water, air-dried and ground into powder for extractions. The methods of extraction used by Agbafor [10] were adopted, utilizing distilled water as solvent. The extracts were concentrated using rotor evaporator to get gel-like dark brown extracts.

2.3 Phytochemical Analysis of the Extracts

The methods of Harbone [11] and Trease and Evans [12] were used to identify the following phytochemicals in the extracts: alkaloids, saponins, tannins, anthraquinones, flavornoids, terpenoids and cardiac glycosides.

2.4 Assessment of Cardioprotective and Antioxidant Properties

2.4.1 Animals and handling

Ethical approval for use of animals in research was given by Ebonyi State University Research and Ethics Committee.

Forty-four adult male albino rats, weighing 132-143 g were brought from the animal house of Biochemistry Department, University of Nigeria, Nsukka. They were placed in eleven groups (A-K) of four rats in each group and kept in animal house of Biochemistry Department, Ebonyi State University Abakaliki for seven days to acclimatize. All the rats were allowed free access to feed (rat chaw) and water before and throughout the experiment.

2.4.2 Animal groups and treatments

Solutions of the extracts were made with distilled water. Different doses of the extracts and 1.2mg/kg body weight of aspirin were given orally to groups A-H and I respectively, while J and K received distilled water for seven consecutive days.

2.4.3 Inducement of cardiotoxicity

On the seventh day, two hours after extract or aspirin administration, groups A-J were treated with a single dose of 2.5 ml/kg body weight of CCl_4 and olive oil (1:1) intraperitoneally. Group K was given distilled water/olive oil (1:1).

Summary of groups and treatment:

Group A -200 mg/kg b. wt leaf extract + CCl_4
Group B -400 mg/kg b. wt leaf extract + CCl_4
Group C -600 mg/kg b. wt leaf extract + CCl_4
Group D – 800 mg/kg b. wt leaf extract + CCl_4
Group E – 200 mg/kg b. wt root extract + CCl_4
Group F – 400 mg/kg b. wt root extract + CCl_4
Group G -600 mg/kg b. wt root extract + CCl_4
Group H- 800 mg/kg b. wt root extract + CCl_4
Group I – 1.2 mg/kg b. wt aspirin + CCl_4
Group J – Distilled water + CCl_4
Group K - Distilled water.

2.4.4 Collection of samples from the animals

Blood samples were collected from the animals following an overnight fast through cardiac puncture under mild anaesthesia using chloroform. The samples were put into specimen bottles without anticoagulant. Heart was also quickly excised, perfused with cold normal saline and homogenized in 0.25M sucrose in phosphate buffer (0.2M, pH 7.4).

2.4.5 Cardioprotective property

Serum levels of CK, LDH, AST, CTnI and lipid profile (total cholesterol, triglycerides, high density lipoproteins and low density lipoproteins) were used to study carditoprotective effect of the extracts. The methods contained in the respective kits (Randox kits, United Kingdom) of the parameters were adopted.

2.4.6 Antioxidant activity

This was assessed by the concentration of the lipid peroxidation product, MDA and antioxidant oxidant enzymes, SOD, CAT and GR in the heart homogenate.

2.4.7 Preparation of heart homogenate

Heart tissues were homogenized in KCl [10 mM] phosphate buffer (1.15%) with ethylene-diamine tetraacetic acid (EDTA pH 7.4) and centrifuged at 12000 rpm for 20 min. The supernatant was used for the measurement of malondialdehyde (MDA),

catalase (CAT), superoxide dismutase (SOD) and glutathione reductase (GR). The method of Ohkawa et al. [13] was used to measure the level of MDA. SOD, CAT and GR activities were determined by the methods of Kakkar et al. [14], Aebi [15] and Bentler [16] respectively.

3. DATA ANALYSIS

Statistical analysis was done using analysis of variance (ANOVA). Means were compared for significance using Duncan's Multiple Range test ($P<0.05$) [17].

4. RESULTS AND DISCUSSION

The phytochemical constituents of the extracts are presented in Table 1. The extracts contained alkaloids, tannins, saponins, flavonoids, anthraquinones, terpenoids and cardiac glycosides in varied proportions. These phytochemicals contribute to the various medicinal applications of leaves and roots of *Newbouldia laevis*. In line with Varadarajan et al. [18], the secondary metabolites (phytochemicals) and other chemical constituents of medicinal plants are responsible for their medicinal values.

Tables 2 and 3 show the cardioprotective effect of the extracts. The levels of CK, LDH, AST and CTnI in the group treated with CCl_4 only (group J) were significantly higher ($P< 0.05$) than those in the untreated group K. The serum concentrations of total cholesterol, triglycerides and LDL were significantly higher ($P<0.05$), while HDL was significantly lower in group J than in group K. Thus, CCl_4 induced heart tissue damage in group J. According to Adaramoye [4], $CCl_4$is known to cause tissue damage by generation of free radicals. The increase the levels of these biomarkers (CK, LDH, AST and CTnI) in serum suggests an increased leakage from cells as a result of toxicity induced by treatment with CCl_4. However, pretreatment of animals with the extracts or aspirin resulted to a significant ($P<0.05$) and dose-dependent prevention of elevation in the levels of CK, LDH, CTnI, AST, total cholesterol, triglycerides and HDL and reduction in HDL. This effect of the extracts and aspirin suggests that they possess cardioprotective activity. Aspirin possesses antiplatelet activity. Platelets, platelet products and thombosis play important roles in the occurrence of acute occlusive vascular events, including myocardial infarction (MI) and ischemic stroke, since the disruption of platelet- and fibrin-rich atheroschlerotic plaque may be followed by aggressive platelet deposition and, ultimately the development of a thrombus that can precipitate an acute occlusive event. The decreased platelet aggregation caused by aspirin is the most plausible mechanism for the cardioprotective effects of the drug [19].

Results of the examination of the antioxidant activity of the extracts are presented in Table 4. There was a significant ($P< 0.05$) increase in heart homogenate MDA levels and decrease in SOD, CAT and GR activities of group J, treated with CCl_4 only relative to the untreated control group. The results were reversed on pretreatment with the extracts. The MDA concentration of the pretreated groups was significantly lower ($P< 0.05$) than the untreated while, the activities of SOD, CAT and GR were significantly higher ($P< 0.05$) in the pretreated groups than in the negative control. These observations, were found to be dose-dependent, are indicative of antioxidant property of the extracts.

Free radical damage and oxidative stress are the major reasons for tissue damage. The antioxidant enzymes are the first-line defense against such damage and thus provide protection against the deteriorating outcome [20]. Oxidative injury and lipid peroxidation can be monitored by measuring liver MDA. Lipid peroxidation is regarded as one of the basic mechanisms of tissue damage caused by free radicals [21].

Group A -200 mg/kg b. wt leaf extract + CCl_4
Group B -400 mg/kg b. wt leaf extract + CCl_4
Group C -600 mg/kg b. wt leaf extract + CCl_4
Group D – 800 mg/kg b. wt leaf extract + CCl_4
Group E – 200 mg/kg b. wt root extract + CCl_4
Group F – 400 mg/kg b. wt root extract + CCl_4
Group G -600 mg/kg b. wt root extract + CCl_4
Group H- 800 mg/kg b. wt root extract + CCl_4
Group I – 1.2 mg/kg b. wt aspirin + CCl_4
Group J – Distilled water + CCl_4
Group K - Distilled water.

Table 1. Phytochemicals present in the extracts

Extract	Saponins	Tannins	Alkaloids	Cardiac glycosides	Terpenoids	Flavonoids	Anthraquinones
leaf	+	++	++	++	++	++	+
root	++	++	+	++	++	++	++

Key: ++ = highly present, + = slightly present

Table 2. Serum levels of CK, AST, LDH and CTnI of the animals after treatment

Group	CK (U/L)	AST(U/L)	LDH (U/L)	CTnI (ng/ml)
A	210.31±2.56^{c}	40.21±3.50^{c}	298.18±5.60^{d}	2.08±0.13^{d}
B	176.60±3.11^{d}	34.60±1.24^{c}	271.42±3.61^{c}	1.70±0.12^{c}
C	171.55±3.60^{d}	30.13±2.45^{c}	264.55±4.20^{c}	1.43±0.14^{c}
D	142.70±2.16^{a}	21.67±1.54^{a}	230.25±1.65^{e}	0.92±0.06^{a}
E	233.17±3.74^{c}	43.70±3.22^{c}	322.14±4.16^{d}	2.20±0.10^{d}
F	201.62±1.62^{c}	41.27±2.50^{c}	301.62±5.10^{d}	1.94±0.12^{d}
G	184.21±4.06^{d}	35.44±1.65^{c}	280.20±3.23^{c}	1.60±0.12^{c}
H	160.03±3.60^{a}	30.45±1.28^{c}	266.71±4.05^{c}	1.15±0.13^{c}
I	167.30±6.12^{a}	28.11±1.63^{d}	276.10 ±5.22^{c}	1.06±0.08^{c}
J	346.34±5.30^{b}	64.20±2.30^{b}	440.65±4.17^{b}	2.70±0.13^{b}
K	153.02±4.11^{a}	20.55±1.23^{a}	257.57±3.55^{a}	0.88±0.07^{a}

Values are mean ± SD, n = 4. Values in the same column having different superscripts differ significantly (P< 0.05)

Table 3. Serum lipid profile of the animals

Group	TC (mg/ml)	TG(mg/ml)	HDL (mg/ml)	LDL (mg/ml)
A	259.35±5.70^{d}	211.36±3.03^{d}	28.11±1.82^{c}	98.30±1.54^{b}
B	248.51±3.67^{c}	187.50±4.15^{c}	33.22±2.02^{c}	80.73±2.50^{c}
C	225.60±6.11^{c}	169.13±2.67^{c}	41.50±1.73^{a}	73.60±1.58^{c}
D	194.33±4.30^{a}	108.30±3.16^{e}	55.45±2.90^{d}	43.52±2.60^{d}
E	273.70±3.04^{d}	228.41±3.06^{d}	22.40±1.70^{c}	102.63±3.20^{b}
F	268.84±3.60^{d}	189.40±4.22^{c}	30.05±3.10^{c}	89.06±4.85^{c}
G	247.45±5.12^{c}	178.32±4.06^{c}	32.32±2.13^{c}	81.36±2.63^{c}
H	228.92±4.08^{c}	133.50±2.85^{a}	43.26±2.55^{a}	57.76±1.70^{a}
I	208.19±4.22^{a}	130.14±3.80^{a}	40.50±3.16^{a}	55.50±1.88^{a}
J	331.60±3.38^{b}	246.70±2.68^{b}	19.62±1.55^{b}	118.34±2.08^{b}
K	203.33±4.13^{a}	120.43±3.03^{a}	44.60±3.36^{a}	52.70±2.64^{a}

Values are mean±SD, n = 4. Values in the same column having different superscripts differ significantly (P< 0.05)

Table 4. Heart levels of MDA, SOD, CAT and GR of the animals

Group	MDA (nmols/g protein)	SOD (U/mg protein)	CAT (U/mg protein)	GR (U/mg protein)
A	20.78±1.68^{c}	6.80±1.06^{c}	87.26±2.22^{c}	5.95±0.56^{c}
B	17.10±2.63^{c}	6.95±0.84^{c}	103.75±4.02^{c}	7.02±1.52^{c}
C	15.03±1.75^{c}	9.37±1.14^{c}	119.26±3.16^{c}	8.62±0.67^{a}
D	7.33±1.08^{a}	13.67±1.03^{a}	139.79±3.70^{a}	10.85±1.02^{a}
E	23.65±1.18^{c}	7.11±0.82^{c}	83.97±3.60^{c}	5.46±0.58^{c}
F	19.05±2.18^{c}	8.02±1.12^{c}	90.52±4.33^{c}	6.64±0.80^{c}
G	15.82±1.09^{c}	8.13±0.75^{c}	113.25±4.06^{c}	8.08±0.55^{a}
H	10.14 ±1.30^{a}	11.25±1.05^{a}	130.23±3.26^{a}	8.95±0.70^{a}
I	10.23 ±1.70^{a}	11.80±0.75^{a}	132.63±3.16^{a}	9.08±1.02^{a}
J	26.40±2.10^{b}	3.16±0.92^{b}	78.65±4.22^{b}	4.60±0.90^{b}
K	9.11±1.13^{a}	13.32±1.43^{a}	148.56±5.67^{a}	11.04±0.83^{a}

Values are mean±SD, n = 4. Values in the same column having different superscripts differ significantly (p< 0.05)

It is probable that the various phytoconstituents of the extracts are involved in scavenging free radicals from tissues, thus, reducing oxidative stress. For example, flavonoids and tannins are phenolic compounds, and plant phenolics are a major group of compounds that act as primary antioxidants or free radical scavengers. Similarly, terpenoids, as vitamins, act as regulators of metabolism and play a protective role as antioxidants [22].

The antioxidant property of the extracts may be responsible for their cardioprotective potential. The findings of this research were found to be consistent with previous reports on medicinal plants used in management and treatment of

cardiovascular disorders by traditional medicine practitioners [23,24]. The effect in the groups treated with leaf extract was significantly different ($P< 0.05$) from that in root extract treated groups. The cardioprotective potential of 800 mg/kg of leaf extract was significantly higher ($P< 0.05$) than that of 1.2 ml/kg of aspirin.

5. CONCLUSION

The presence of the identified phytochemicals in the extracts partly explains the medicinal applications of leaves and roots of *Newbouldia laevis*. The exact compounds responsible for the observed pharmacological activities are under investigation. The cardioprotective potential may be as a result of the antioxidant property of the phytoconstituents. However, this is subject to further examination. Our findings may be useful in explaining the use of leaves and roots of *Newbouldia laevis* in management and treatment disorders of the cardiovascular system.

CONSENT

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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