

Protective Effect of Methanol Extract of Christmas Bush (*Alchornea cordifolia*) Leaves Against Sodium Arsenite Induced Hepatotoxicity in Wistar Rats

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ABSTRACT

Background and Objective: Liver diseases are among the most serious ailments and are mainly caused by toxic chemicals excess, consumption of alcohol, infections and autoimmune/disorders. *Alchornea cordifolia* plant is used for urinary, respiratory, liver and gastrointestinal disorders. This study evaluated the hepatoprotective effect of *Alchornea cordifolia* leaf extract on sodium arsenite-induced liver toxicity in male Wistar rats. **Materials and Methods:** Phytochemical screening and antioxidant activities were determined using standard methods. Thirty-five Wistar rats were randomly distributed into 7 groups: Group 1 (feed and distilled water only), Group 2 (sodium arsenite only), Group 3 (sodium arsenite and 200 mg of *Alchornea cordifolia* extract), Group 4 (sodium arsenite and 400 mg of *Alchornea cordifolia* extract), Group 5 (sodium arsenite and 200 mg of silymarin), Group 6 (200 mg of *Alchornea cordifolia* extract) and Group 7 (400 mg of *Alchornea cordifolia* extract). Blood samples collected from the experimental animals were subjected to hematological analysis and liver function tests. **Results:** The phytochemical screening result of the methanolic extract of *Alchornea cordifolia* showed the presence of saponin, flavonoids, alkaloids, phenol and anthraquinones. The total antioxidant content, total phenolic capacity, ferric reducing assay power, 2,2 diphenylpicrylhydrazyl of methanolic extract of *Alchornea cordifolia* reveals high antioxidant activity concerning the increasing concentration. **Conclusion:** The hematological parameters, liver function test and histopathological examination of the methanolic extract of *Alchornea cordifolia* possess a hepatoprotective effect which may be due to the strong antioxidant activity of the methanolic extract of *Alchornea cordifolia*. Therefore, liver disorders may be managed using methanolic extract of *Alchornea cordifolia*.

KEYWORDS

Cancer prevention, phytochemicals, hepatotoxicity, antioxidant activities, *Alchornea cordifolia*, sodium arsenite

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INTRODUCTION

Amongst the numerous approaches employed in combatting ailments is the use of medicinal plants for the treatment of various diseases¹. Plants contain numerous antioxidants that help to confer protection against free radicals-associated diseases². *Alchornea cordifolia* plant is of great importance to the health of individuals and communities³. It is commonly used as a medicinal plant throughout its area for the treatment of cancer, inflammatory disorders, bacteria and parasitic disorders, the treatment of gastrointestinal and urinary disorders, ulcers and wounds. The leaves are mostly used, but also the stem bark, stem pith, leafy stems, root bark, roots and fruits enter in local medicine. An estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020, with 56% of cancer cases and 63% of cancer deaths occurring in the less developed regions of the world⁴. Liver diseases are responsible for the death of about 2 million people yearly throughout the world especially in developing nations, where access to quality health delivery systems is limited⁵. The liver is susceptible to the harmful effects of infectious agents including viruses and the toxicities of drugs mainly because of their involvement in biotransformation and elimination of toxins from the body. Several researchers have used silymarin as a reference therapy for hepatoprotection against hepatotoxicity⁶.

Despite the progressive advance in conventional cancer treatments, medicinal plants with natural origins still offer promising options and have been recognized for their therapeutic effects with fewer adverse effects⁷. Arsenic is a naturally occurring metalloid element that is widely found in both organic and inorganic forms in the environment. It is present in the earth's crust and can be found in water, food, soil and air⁸. Arsenic is rapidly absorbed from the gastrointestinal tract and lungs and is widely distributed in most tissues while large amounts are deposited in the liver, kidney, lungs and skin⁹.

There is a lack of satisfactory liver protective drugs in orthodox medical practice for serious liver disorders. Herbal drugs play a role in the management of various liver disorders most of which speed up the natural healing processes of the liver. Scientific studies have confirmed the pharmacological activities of many medicinal plants and their bioactive compounds. Plants contain numerous antioxidants which help to confer protection against free radicals-associated diseases². However, little or low research has been carried out on the hepatoprotective effect of *Alchornea cordifolia* against sodium arsenite. Hence, this present study was undertaken to assess the hepatoprotective and antioxidant activities of *Alchornea cordifolia* leaf extracts in rats against sodium arsenite as a hepatotoxin to prove its claims in folklore practice against liver disorders. The preliminary phytochemical analysis of the extract was also carried out.

MATERIALS AND METHODS

Sample collection: The 2000 g of fresh leaves of the plant *Alchornea cordifolia* were collected from a farm in Bode Market, Ibadan and were identified and authenticated by a plant taxonomist at the Department of Botany Herbarium, University of Ibadan, Oyo State. A whole flowering plant of *Alchornea cordifolia* was deposited in the herbarium and assigned voucher number 23257. The study was carried out from April to September, 2023.

Experimental protocol: The study was conducted with 35 rats, 12 weeks old healthy male albino Wistar rats with an average weight of about 140 g. They were purchased after physical and behavioral veterinary examination at the Department of Physiology, University of Ibadan, Ibadan, Nigeria. The rats were fed with commercially available rat chow (Top Feeds Nigeria Limited) and clean water *ad libitum*. A week after acclimatization; the rats were separated into seven groups of five rats each as follows: Group 1 was fed with distilled water, Group 2 was 10 mg/kg of sodium arsenite only, Group 3 was 10 mg/kg of sodium arsenite+200 mg/kg of methanolic extract of *Alchornea cordifolia* leaves, Group 4 was 10 mg/kg of sodium arsenite+400 mg/kg of methanolic extract of *Alchornea cordifolia* leaves, Group 5 was 10 mg/kg of sodium Arsenite+200 mg/kg of silymarin, Group 6 was 200 mg/kg of methanolic extract of *Alchornea cordifolia* leaves only and Group 7 was 400 mg/kg of methanolic extract of *Alchornea cordifolia* leaves only.

Phytochemical screening: The phytochemical screening of the different extracts was carried out using the standard procedures as described by Sofowara¹⁰. Total alkaloids, flavonoids and saponins were quantitatively determined using the method described by Krishnaiah *et al.*¹¹.

In vitro antioxidants activities: In order to evaluate the antioxidant potential through free radical scavenging by the test samples, the change in optical density of DPPH radicals was monitored. According to Manzocco *et al.*¹², total phenolic compound contents were determined using the Folin-Ciocalteu method (Journal of Pharmacology and Phytochemistry, 2017) and Ferric ions reducing power was measured according to the method of Oyaizu¹³. Total antioxidant activity was estimated by phosphomolybdenum assay¹⁴.

Hematology test: The uncoagulated blood was analyzed for the following; Packed Cell Volume (PCV), White Blood Cell Count (WBC), Neutrophils, Eosinophils, Lymphocytes and Monocytes were determined using Automated Haematologic Coulter Analyser (Beckman Coulter, California, USA) in accordance with the procedure of Zandecki *et al.*¹⁵.

Liver function test: The following liver function tests were conducted to investigate derangement in the liver of the animals used for the study; Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) and total protein were determined by the colorimetric method using a commercial assay kit from Randox Laboratories Ltd., Co., Antrim, United Kingdom. Alkaline Phosphatase (ALP) was estimated by the colorimetric method using assay kits from TECO Laboratories Ltd as described by Akcakaya *et al.*¹⁶.

Statistical analysis: Data were displayed as averages and standard errors of the average. They were analyzed by One-way Analysis of Variance (ANOVA) using the 17th version of SPSS. For each parameter, the variation between the average of the control and test groups was assessed using the Duncan's Multiple Range Test. The level of significance was set at $p < 0.05$.

RESULT

Phytochemical screening of *Alchornea cordifolia* extract: The result of phytochemical screening for the hexane fraction, ethylacetate fraction and methanol fraction revealed the presence of chemical constituents such as phenols, alkaloids, tannins, saponins, anthraquinones and flavonoids presented in Table 1 and 2.

In vitro antioxidant activities of methanol extract of *Alchornea cordifolia*: The *in vitro* antioxidant activities of *Alchornea cordifolia* increased with increasing concentration. The results showed that the order of total antioxidant, total phenolic capacity, ferric reducing assay power and 2,2 diphenylpicrylhydrazyl activities were observed to be concentration-dependent as presented in Table 3.

Effect of extract on liver enzymes: The protective effect of *Alchornea cordifolia* leaf extract was assessed by evaluating the activities of serum enzymes; Alkaline Phosphatase (ALP), Aspartate Amino Transferase (AST), Alanine Amino Transferase (ALT) and total protein (TP) in the groups of rats administered the extract and/or sodium arsenite and the control untreated rats. The results presented in Table 4 revealed that sodium arsenite elevated the serum level of AST, ALT and ALP in Group 2 when compared to the normal control (group 1). However, administration of extract in the group caused a significant reduction.

Effect of *Alchornea cordifolia* leaf extract on hematological parameters: The effects of graded doses of *Alchornea cordifolia* leaf extract on hematological indices (PCV, WBC, Neutrophils and Lymphocyte counts) as presented in Table 5 revealed that the SA only treated rats showed a significant reduction ($p < 0.05$) in PCV when compared to the control group. However, pretreatment with the different doses of the extract increased the PCV value towards that of distilled water thereby suggesting that extract can

Table 1: Qualitative analysis of phytochemical constituents for hexane fraction, ethylacetate fraction and methanol fraction of *Alchornea cordifolia*

Test	Hexane fraction	Ethylacetate fraction	Methanol fraction
Saponins	-ve	++ve	++ve
Tannins	-ve	+ve	+ve
Flavonoids	+ve	++ve	++ve
Cardiac glycosides	+ve	+ve	+ve
Anthraquinones	+ve	+ve	++ve
Terpenoids	+ve	+ve	+ve
Steroids	-ve	+ve	+ve
Alkaloids	+ve	++ve	++ve
Phenol	-ve	++ve	++ve

++ve: Moderately present, +ve: Present and -ve: Absent

Table 2: Quantitative analysis of phytochemical constituents for hexane fraction, ethylacetate fraction and methanol fraction of *Alchornea cordifolia*

Sample	Hexane fraction	Ethylacetate fraction	Methanol fraction
Alkaloids	0.45	1.70	1.60
Flavonoids	0.22	4.46	3.05
Saponins	0.00	1.40	1.95
Tannin	0.00	0.30	0.32
Terpenoid	1.35	0.08	0.50
Phenol	0.00	0.77	1.09

Values are Mean±SD (n = 3) of triplicate determinations. Conventional units, GAE: Gallic acid equivalent for phenolics

Table 3: Antioxidant determination of methanol extract of *Alchornea cordifolia*

Concentration (µg/mL)	TAC	TPC	FRAP	DPPH
200	0.34±0.001	0.95±0.003	0.98±0.002	0.45±0.003
400	0.36±0.003	1.32±0.002	1.00±0.001	0.42±0.001
600	0.40±0.002	1.63±0.004	1.22±0.001	0.41±0.001
800	0.41±0.001	1.63±0.004	1.43±0.003	0.39±0.001
1000	0.42±0.001	2.33±0.003	1.50±0.003	0.36±0.00

Values are presented as Mean±Standard Deviation, CONC: Concentration, TAC: Total antioxidant content, TPC: Total phenolic capacity, FRAP: Ferric reducing assay power and DPPH: 2,2-Diphenyl-1-picrylhydrazyl

Table 4: Effects of *Alchornea cordifolia* leaf methanol extracts on serum biochemical indices of rats

Group	Treatment	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	TP (g/dL)
1	Distilled water	20.40±0.54	70.20±5.31	40.60±0.89	5.28±0.47
2	SA	46.25±6.13 [#]	156.25±10.34 [#]	88.50±3.11 [#]	10.30±1.62 [#]
3	SA+200 mg/kg extract	34.67±8.39 [*]	87.00±11.53 [*]	43.67±2.52 [*]	4.90±1.73 [*]
4	SA+400 mg/kg extract	31.33±2.51 [*]	77.33±18.77 [*]	40.67±1.16 [*]	5.9±1.00 [*]
5	SA+200 mg/kg silymarin	27.67±1.16 [*]	100.00±14.18	44.00±4.58 [*]	6.87±1.67
6	200 mg/kg extract	33.60±1.82	80.00±7.31	41.00±0.71	6.46±3.20
7	400 mg/kg extract	21.80±1.92	105.20±6.91	47.20±4.66	7.66±3.40

SA: Sodium arsenite, (values are Mean±SD), [#]Mean difference is significant (p<0.05) when compared with control (group 1), ^{*}Mean difference is significant (p<0.05) when compared with group treated with SA alone (group 2), ALT: Alanine Transaminase, AST: Aspartate Aminase, ALP: Alkaline Phosphatase and TP: Total proteinTable 5: Effect of methanol leaf extracts of *Alchornea cordifolia* on the haematological parameters on whole blood of rats

Group	Treatment	PCV (%)	WBC (×10 ³ /µL)	NEU (%)	LYM (%)
1	Distilled water	55.80±3.83	3.72±0.39	38.00±6.71	58.6±8.50
2	SA	18.75±3.693 [#]	17.13±2.50 [#]	47.25±10.60	70.00±7.07 [#]
3	SA+200 mg/kg extract	35.67±5.13	6.23±0.71	43.33±5.77	58.33±10.41
4	SA+400 mg/kg extract	34.67±5.77 [*]	4.37±0.85 [*]	41.33±8.89	56.67±10.41 [*]
5	SA+200 mg/kg silymarin	35.33±11.02 [*]	5.57±2.27 [*]	34.33±12.10	62.67±9.45 [*]
6	200 mg/kg extract	45.80±4.21	5.34±1.66	40.00±13.69	58.00±14.83
7	400 mg/kg extract	44.80±3.70	5.32±0.95	38.40±5.94	60.60±4.39

SA: Sodium arsenite, (values are Mean±SD) [#]Mean difference is significant (p<0.05) when compared with control (group 1), ^{*}Mean difference is significant (p<0.05) when compared with group treated with SA alone (group 2). PCV: Packed Cell Volume, WBC: White Blood Cell, NEU: Neutrophils and LYM: Lymphocytes

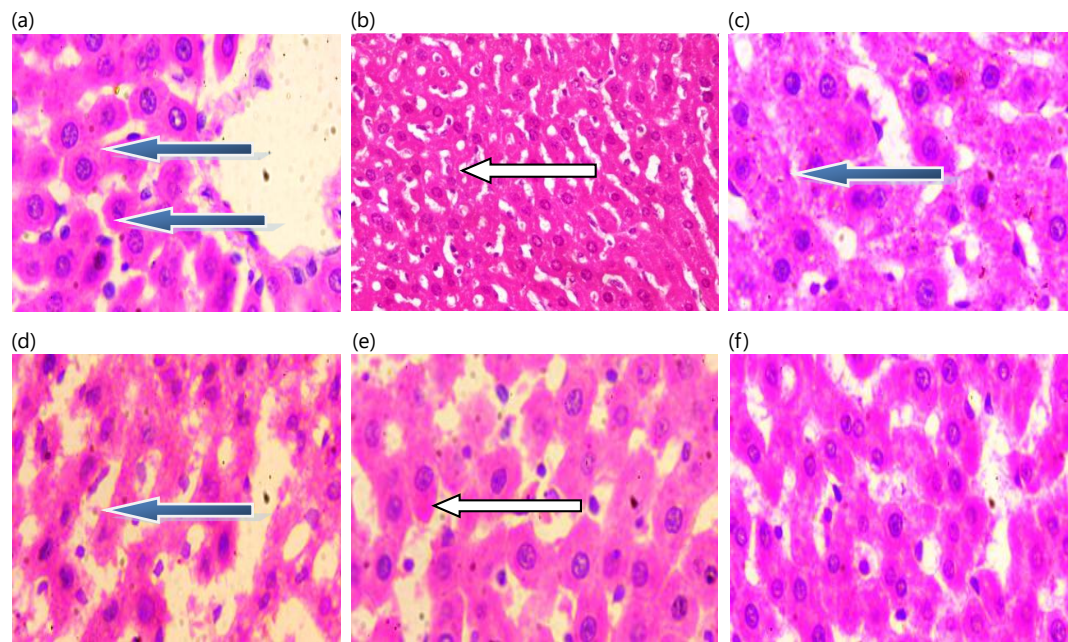


Fig. 1(a-f): Photomicrograph of liver sections rats treated with *Alchornea cordifolia* and sodium arsenite, (a) SA (2.5 mg/kg body weight) showing diffused degeneration of hepatocytes, portal congestion, fibrotic changes and periportal cellular infiltration by mononuclear cells, (b) *Alchornea cordifolia* (200 mg/kg)+SA (2.5 mg/kg) showing very mild vacuolar degeneration of hepatocytes, (c) *Alchornea cordifolia* (400 mg/kg)+SA (2.5 mg/kg), (d) SA+200 mg/kg silymarin showing very mild vacuolar degeneration of hepatocytes, (e) Control showing no visible lesion and (f) *Alchornea cordifolia* only shows no visible lesions

ameliorate anemic condition induced by SA. There was a significant increase ($p < 0.05$) in WBC and lymphocytes of the SA treated group when compared to the control groups. The increase in WBC and lymphocytes may be due to oxidative stress generated by SA. The administration of the extract and exposure to SA did not have any statistically significant effect ($p < 0.05$) on the neutrophils level. This indicates that *Alchornea cordifolia* extract may boost the immune system against SA induced immunotoxicity.

The results of the histological assessment of the liver cell integrity support the serum enzyme activity patterns of hepatotoxicity in the treated animals as presented in Fig. 1a-f. There was marked diffused degeneration of hepatocytes, portal congestion, fibrotic changes and periportal cellular infiltration by mononuclear cells in the liver of rats administered sodium arsenite (positive control). There was no visible lesion in the negative control group and the groups administered with extract only. However, pretreatments with the extract showed very mild vacuolar degeneration of hepatocytes in the liver of experimental rats.

DISCUSSION

Exposure to arsenic via the intake of contaminated water has been linked with diverse health defects like certain forms of cancer, skin lesions and non-cancer health effects such as neurological disorders and impaired cognitive development in children¹⁷. Related findings have been documented by Shiblur Rahaman *et al*¹⁸. The qualitative screening of the phytochemical constituents of the hexane fraction, ethylacetate fraction and methanol fraction of *Alchornea cordifolia* leaves showed significant amounts of tannins, alkaloids, flavonoids and saponins. Hexane fraction showed the presence of flavonoids, cardiac glycosides, anthraquinones, terpenoids and alkaloids while saponins, tannins, steroids

and phenol were absent. Ethylacetate fraction showed the presence of saponin, flavonoids, alkaloids and phenol in abundance, while tannins, cardiac glycosides, anthraquinones, terpenoids and steroids were moderately present. Methanol fraction showed the presence of saponin, flavonoids, anthraquinones, alkaloids and phenol in abundance, tannins, cardiac glycosides and terpenoids were moderately present while steroids were absent. Tannins and related compounds prevent the destructive effects of lipid peroxide in liver cells by lowering the levels of lipid peroxide in liver cells. Tannins has also been reported to have anti-inflammatory and antiulcer property in rodents, showing a strong antioxidant property¹⁹.

The antioxidant determination of hexane extract shows a progressive increase in absorbance as the concentration of hexane fraction for total phenol content, total antioxidant capacity and ferric reducing assay power increases while 2,2-Diphenyl-1-Picrylhydrazyl (DPPH) decreases as the concentration of hexane fraction increases. Thus, total phenol content (TPC), total antioxidant capacity (TAC) and ferric reducing assay power (FRAP) obey Beers's Lambert law. This implies that the methanol extract reveals highly potent activity concerning the increasing concentration. In the present study, the strong inhibition of the DPPH free radicals by the hexane fractions of the leaf extract of *Alchornea cordifolia* which is comparable to that of standard antioxidant (ascorbic acid) indicates that the plant possesses strong antioxidant activity. Thus, it is possible that other secondary metabolites of the plant as observed in the present study and earlier studies may be responsible for the antioxidant and hence the hepatoprotective activity of the plant²⁰.

The liver is an important target organ for arsenic toxicity²¹. Arsenic intoxication in experimental animals has been linked with micronucleus formation and hepatic tumors²². Aspartate Aminotransferase (AST) and Alanine Aminotransferase (AST) are members of the transaminase family of enzymes. They are also known as aminotransferases; they catalyze the transfer of amino groups between L-alanine and glutamate for physiological purposes. The ALT and AST are found in large amounts in the liver and also small amounts are found in the heart, kidney and muscles. When the liver is injured or inflamed as the case may be via its exposure to various forms of toxic substances, the level of ALT and AST in the blood is usually elevated. The level of these enzymes in the blood is directly related to the extent of the tissue damage²³. The results obtained from the assessment of the serum levels of AST, ALT and ALP indicate that sodium arsenite significantly ($p < 0.05$) increased the enzymes activity when compared to control group. This is suggestive of hepatocytes protection from *Alchornea cordifolia*. Pre-treatment against SA-induced damages. This can be attributed to the antioxidants present in *Alchornea cordifolia*. This is by some recent studies that recommend the use of antioxidants and antioxidant-rich foods and herbal medicinal plants for the management of arsenicosis^{24,25}. The activities of all the liver enzymes (GGT, AST, ALT and ALP) were significantly low in the *Alchornea cordifolia* only-treated group confirming protective properties. The observations made here are consistent with the findings from Tokar *et al.*²². Histological examinations of liver sections of treated animals showed that SA was potentially hepatotoxic as reflected by portal congestion, fibrotic changes and periportal cellular infiltration by mononuclear cells. In the group that was treated with sodium arsenite only (Group 2), there was a marked diffused degeneration of hepatocytes, portal congestion, fibrotic changes and periportal cellular infiltration by mononuclear cells in the liver of rats administered sodium arsenite (positive control) which indicates the necrotic cell death of the hepatocytes. This was consistent with earlier reports on the hepatotoxicity of sodium arsenite²⁶. However, the liver sections from SA and *Alchornea cordifolia* treated group exhibited very mild hepatic degeneration though the *Alchornea cordifolia* treated group showed no visible lesions confirming a modulatory effect of *Alchornea cordifolia* on SA-induced hepatocytes damage.

Therefore, methanol extract of *Alchornea cordifolia* showed potent hepatoprotective activity in sodium arsenite induced toxicity in rats. This effect may be attributed to the antioxidant principles present in the plant such as tannins and saponins. Further identification and the elucidation of the structures of the actual constituents responsible for this activity are underway.

CONCLUSION

The present study demonstrated that methanol extract of *Alchornea cordifolia* contains a substantial number of bioactive phytochemicals and that the extract ameliorated sodium arsenite induced toxicity in albino Wistar rats. Findings suggest that methanol extract of *Alchornea cordifolia* could be a promising therapeutic agent for managing hepatotoxicity through characterization of the extract.

SIGNIFICANCE STATEMENT

Arsenic contamination is a major public health challenge requiring urgent corrective measures and also its toxicity has been linked to cancer in both experimental animals and humans. Chemoprevention using medicinal herbs and dietary antioxidants approaches has been suggested to offer a good potential in the treatment and management of arsenic toxicity. Hepatotoxicity has increased as a result of various environmental toxins and hepatotoxic drugs. Due to the absence of efficient liver-protective drugs in modern medicine, a large number of studies searching for hepatoprotective constituents from natural sources have been conducted in recent years.

Furthermore, considering the toxic effects associated with the use of synthetic chemicals in cancer therapy, scientific research efforts are being geared toward naturally occurring plant sources that are therapeutically effective, culturally acceptable and economically accessible. However, there is a dearth of information on the protective effect of *Alchornea cordifolia* extract on SA-induced toxicity. Hence the findings of this study may pave the way for the development of novel treatments for inflammatory conditions and mitigating arsenicosis, thereby advancing medical knowledge and providing valuable insights into the utilization of natural compounds as alternative and complementary approaches in modern medicine, thereby enhancing overall health outcomes.

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