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Effect of Ethanol Extract of *Alchornea cordifolia* Treatment on Lipid Profile, HMG CoA Reductase, and Lipase Activities in Bisphenol A (BPA) Induced Obese Wistar Rats

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ABSTRACT

Bisphenol A (BPA) is a high-production volume chemical widely used as a monomer in plastics and known for its endocrine-disrupting properties. Exposure to BPA has been associated with obesity and other metabolic disorders through its effects on lipid metabolism, adipogenesis, and hormonal regulation. Medicinal plants with proven pharmacological activities are being explored as safer alternatives for managing such conditions. *Alchornea cordifolia*, a plant commonly used in African ethnomedicine, has been reported to possess antioxidant, anti-inflammatory, and anti-diabetic properties. This study investigated the effect of the ethanolic extract of *A. cordifolia* on adipose tissue weight, liver weight, lipid profile, lipase activity, and HMG-CoA reductase activity in BPA-induced obese Wistar rats. Obesity was induced by administering BPA (50 µg/ml), followed by treatment with graded doses of *A. cordifolia* extract. The results showed that BPA administration significantly increased adipose tissue and liver weights, as well as altered lipid profiles in young male Wistar rats.

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Treatment with *A. Cordifolia* extract significantly reduced these changes, demonstrating anti-hypercholesterolemic and antihyperlipidemic effects. Among the tested doses, 1000 mg/kg of the ethanolic extract exhibited the greatest efficacy in mitigating BPA-induced obesity.

***Keywords*:** obesity, endocrine disruptor, ethnomedicine, lipid profile, adipose tissue, HMG-CoA reductase.

1. INTRODUCTION

The incidence of obesity has risen over the last few decades, and the mechanisms remain to be illustrated. Obesity increases the risk of serious health conditions such as non-alcoholic fatty liver disease (NAFLD), cardiovascular disorders, and cancer, amongst others (J Mol Cell Biol. 2021). Researchers have shown that some chemicals in food and the environment, known as endocrine-disrupting chemicals (EDCs), can play a role in the rise of obesity and other metabolic problems (Amato et al., 2021). Exposure to these chemicals during pregnancy or early life may change the way the body's metabolism develops, making people more likely to develop obesity and metabolic syndrome later (Singh & Li, 2021; Núñez-Sánchez et al., 2023). These effects often involve small changes in gene regulation, such as DNA methylation, that can influence how fat cells form and store energy (Toledano et al., 2024). Overall, this means that early contact with synthetic chemicals like bisphenols may combine with other risk factors to increase the chances of obesity across the lifespan (Hsu & Tain, 2021).

Bisphenol A (BPA), an endocrine disruptor, is a carbon-based chemical commonly used in the production of plastics. It is one of the highest volume chemicals produced worldwide, which is prevalent in our environment. Ingestion, inhalation, or skin contact can increase both the number and size of fat cells and impair how fat tissue responds to insulin and other hormonal signals (Kassotis et al., 2021). BPA is lipophilic and can accumulate in adipose tissue, where it may promote the growth and proliferation of fat cells and interfere with insulin and hormonal regulation of adipose function, ultimately suggesting that it's an obesogenic that elicits abnormal fat accumulation leading to obesity (Hong et al., 2023). Adipose tissue functions not only as a fat store but also as an endocrine organ that secretes hormones like leptin and adiponectin, which signal the state of energy reserves and regulate insulin sensitivity. Adipokines have been reported to be marred by BPA exposure, altering the secretion and gene expression of key adipokine hormones, thus impairing normal metabolic regulation. These changes are thought to contribute to insulin resistance, inflammation, and fat deposition (González-Casanova et al., 2023). Obesity disrupts this balance, increasing leptin and decreasing adiponectin, which contributes to insulin resistance (Murakami et al., 2022; El Amrousy et al., 2022). Recent evidence also suggests that HMG-CoA reductase inhibitors may influence metabolic functions beyond cholesterol reduction, affecting adipose tissue metabolism, β-cell function, and systemic insulin sensitivity (Sarsenbayeva et al., 2021).

Plants produce a wide range of secondary metabolites that show strong biological and pharmaceutical effects, including antioxidant, anti-inflammatory, and antimicrobial (Elshafie, Camele, & Mohamed, 2023). *Alchornea cordifolia* is a well-known African medicinal plant traditionally used for various healing purposes. Recent studies on *Alchornea cordifolia* have confirmed that the plant has strong anti-inflammatory, hepatoprotective, and antidiabetic effects. For example, Oruka & Achuba (2023) found that the aqueous leaf extract exhibits antioxidant and anti-inflammatory activities in dose dependent ways.

The methanolic leaf extract showed significant inhibition of pancreatic lipase in vitro, which points to potential anti-obesity action (Eboh & Ebizimor, 2021). In a high-fat diet obesity model, ethanol extract of *A. cordifolia* significantly improved lipid profiles, reduced body weight gain, and modulated HMG-CoA reductase and other metabolic enzymes. These newer findings align with older reports, expanding our understanding of how their phytochemical constituents, like flavonoids, phenolics, and alkaloids, might help reduce fat accumulation and improve adipose tissue function. Several studies have been reported to develop plants with anti-obesity effects, such as *Curcuma longa*, *Radix platycodi,* etc. These plants have been reported to reduce obesity due to their ability to minimize the activity of triacylglycerol, cholesterol, HmG CoA reductase, and lipase activity, enzymes involved in cholesterol and fatty acid biosynthesis, respectively. Although the anti-hyperlipidemic property of *Alchornea cordifolia* has been assessed and reported (Thompford *et al.,* 2015), there is no scientific information regarding the ethanol extract of *Alchornea cordifolia* treatment on lipid profile, HMG CoA, and lipase activities in Bisphenol A(BPA) induced obese Wistar rats. The aim of this study is to determine the effect of ethanol extract of *Alchornea cordifolia* treatment on lipid profile, HMG CoA reductase, and lipase activities in Bisphenol A (BPA) induced obese Wistar rats.

2. MATERIALS AND METHODS

Chemicals and Reagents

The Bisphenol A (2,2-bis(4-hydroxyphenyl) propane) in the form of pure pellets and the reagents used are of analytical grades, mainly obtained from Sigma Aldrich Company, UK, through Bristol Scientific.

Extraction of *A.Cordifolia* Seed

A.cordifolia leaves were obtained from Uyo, Akwa Ibom State. Thereafter, the leaves were authenticated in the Department of Plant and Ecological Studies, Faculty of Biological Sciences, University of Calabar, Calabar, and given a voucher number. The leaves were washed, air-dried, and then milled into powder using a manual blender. Powdered leaves were extracted with ethanol (using a Soxhlet apparatus). The solvent in the extract was evaporated using a rotary evaporator and a water bath (50°C). The extract was weighed, and the percent yield calculated thus: Weight of extract / Weight of starting material X 100.

Experimental Animals

Young male Wistar rats (80-100g) were obtained from the Animal House, Department of Biochemistry, Faculty of Basic Medical Sciences, University of Calabar, Calabar, Cross River State. The study animals were acclimatized to the formulated diet for one (1) week, and water was given ad libitum. After acclimatization, the animals were assigned to control and test groups and treated as shown in the experimental design (Table 2). The procedures were approved by the Faculty of Basic Medical Sciences Animal Ethics Committee, University of Calabar, Calabar.

Table 1. Composition of high-fat diet.

Ingredients	Percentage composition (per 100g)
Normal feed	64
Lard	15
Sucrose	10
Milk	5
Egg yolk powder	5
Sodium chloride	0.2
Porcine bile salt	0.8

Table 2. Experimental Design.

Cage numbers	Animal grouping	Treatment
1	Normal control	Commercial feed and water only
2	BPA only	Commercial feed and 50µg/ml of BPA
3	BPA + Orlistat	30mg/kg of Orlistat
4	BPA + *A. cordifolia* (500mg/kg)	500mg/kg of ethanol extract of A.C.
5	BPA + *A. cordifolia* (1000mg/kg)	100mg/kg of ethanol extract of A.C.

Dietary Induction of Obesity

The animals were acclimatized for two (2) weeks (Week 1 Normal diet; Week 2- HFD). For four weeks, the test animals were placed on a formulated high-fat diet (HFD) as well as received water freely to establish the obesity induction process. All groups, except Normal control (which will receive commercial feed and water), and HFD only (which will receive the formulated diet), were exposed daily to BPA (50 µg/kg per os, ≥99% purity, Sigma-Aldrich, Milan, Italy).

Animal Handling, Sacrifice/Tissue Sample Collection, and Preservation

The experimental design showing obesity induction and treatment is shown in Table 2. The experimentally obese animals were separated into four new groups comprising six Wistar rats and six normal rats and given the treatments outlined in Table 2. The rats were kept in a room with a temperature of 25 °C ± 3 °C and fed rat pellets and tap water as needed. Upon initiating treatment, the animals' weights and fasting blood glucose (FBG) levels were assessed. These measurements were repeated weekly and biweekly for six (5) weeks. Whereas the fasting blood glucose was measured weekly using One Touch® glucometer, feed/energy intake and body weights were measured weekly with a digital weighing balance.

Biochemical Assays

Determination of Total Cholesterol (T.C.) Concentration

The serum level of T.C. was quantified by spectrophotometric methods as described by Stein (1987) using the Randox® kit (Randox Laboratories Limited, U.K.).

Determination of Serum Triacyl Glycerides (T.G.) Concentration

The serum level of T.G. was determined by the enzymatic method described by Stein (1987) using the Randox® kit (Randox Laboratories Limited, U.K.).

Determination of Serum High-Density Lipoprotein Cholesterol (HDL-C) Concentration

The HDL-c level was determined using the Randox® kit (Randox Laboratories Limited, U.K.) based on the method described by Naito (2003).

Determination of Low-Density Lipoprotein- Cholesterol (LDL-C) Concentration

The serum level of LDL-c was calculated according to the protocol of Friedewald (1972) using the equation:

LDL-c (mg/dl) = TC – TG/5 – HDL-c

Evaluation of Hydroxylmethylglutaryl (HMG)-Coa Reductase Activity In Liver Homogenates

Sample preparation: Tissue for indirect determination of HMG-CoA reductase activity was extracted using the method of Venugopala and Ramakrishnan (1975).

Principle

In this indirect method, variation in 3-hydroxy-3-methylglutaryl-coenzyme A reductase (NADPH) activity in liver tissue is assessed using the 3-hydroxy-3-methylglutaryl-CoA and mevalonate concentrations in the tissue homogenate by estimating the terms of absorbances. The ratio between the two is taken as an index of the activity of the enzyme, which catalyzes the conversion of 3-hydroxy-3-methylglutaryl-CoA to mevalonate.

The ratio increases under conditions in which the activity of this enzyme in the liver reportedly decreases (e.g., fasting, cholesterol feeding, and the effect of statins and related compounds) and decreases under conditions in which the activity of this enzyme reportedly increases (high-energy diets). HMG-CoA was determined by reaction with hydroxylamine at weakly acidic pH and subsequent colorimetric measurement of the resulting hydroxamic acid by formation of complexes with ferric salts. Because mevalonate interferes in this estimation at acid or neutral pH, alkaline hydroxylamine was used to estimate specifically HMG-CoA only, and interference by coenzyme A is also minimal when reading was taken at 540 nm.

Determination of The Magnitude of Cholesterol Synthesis (MCS)

The magnitude of cholesterol synthesis per gram liver weight of fresh wet tissues was determined by dividing the fresh weight of the entire animal liver by TMAR and multiplying by 100.

The result was reported as percentage mevalonic acid synthesis per gram liver weight, thus:

Where:

MCS = Magnitude of Cholesterol Synthesis (MCS)
TMAR = Tissue Mevalonic Acid Ratio

Percentage Reduction In HMG-Coa Reductase Activity

This was calculated as 100 - MCS%

Where MCS = Magnitude of cholesterol synthesis.

Statistical Analysis

Statistical analyses were carried out using SPSS version 22. Results were expressed as mean ± standard deviation (SD). The various data were subjected to one-way analysis of variance (ANOVA), and the differences between the samples were determined by Duncan's multiple range test, setting P values at 0.05.

3. RESULTS AND DISCUSSIONS

Effect of *A. Cordifolia* Treatment on Wistar Rats After BPA Administration.

The result obtained from this study showed that the administration of BPA caused a significant ($p<0.05$) increase in the weight of the adipose tissue indicated in the obese control (2.49g ±0.15) compared to the normal control group (1.16g ±0.30)**.** Treatment with orlistat significantly ($p<0.05$) reduced the weight of adipose tissues (1.27g ±0.17), while treatment with (500mg/kg) of *A. cordifolia* (2.07g ±0.54) showed no significant difference. However, treatment with *A. cordifolia* (1000mg/kg) showed a more significant reduction in adipose tissue (1.52g ±0.07) weight compared to the obese control (2.49g ±0.15) (Figure 1). With regards to the liver, BPA administration resulted in a significant increase in the liver weight of the obese control (7.62g ±0.17) compared with the normal control (5.07g ±0.17).

Moreover, treatment with orlistat, 500mg/kg, and 1000mg/kg of *A.cordifolia* significantly ($p<0.05$) reduced liver weight (5.29g ±0.05, 5.11g ±0.25) compared with obese control (7.62g ±0.17). Additionally, 1000mg/kg treatment had the most significant ($p<0.05$) effect on the liver weight of all *A. cordifolia*-treated rats (Figure 2).

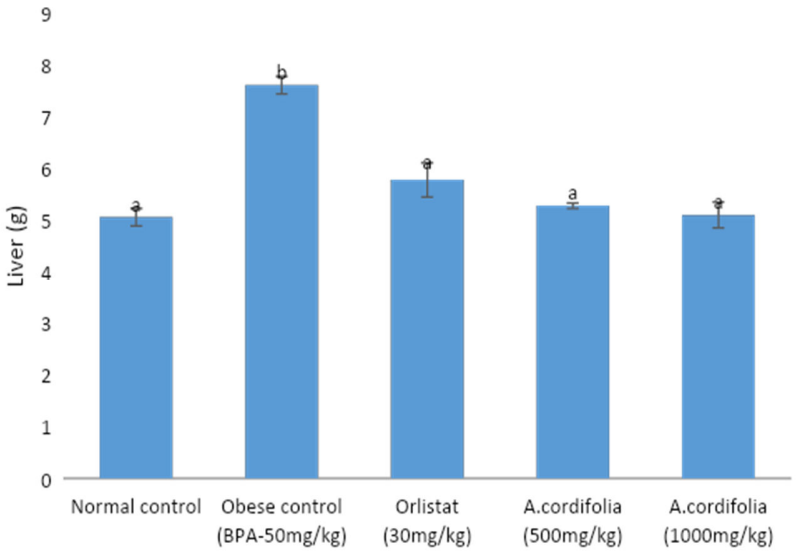

Figure 1. Effect of *A. cordifolia* treatment on liver of BPA induced obese Wistar rats.

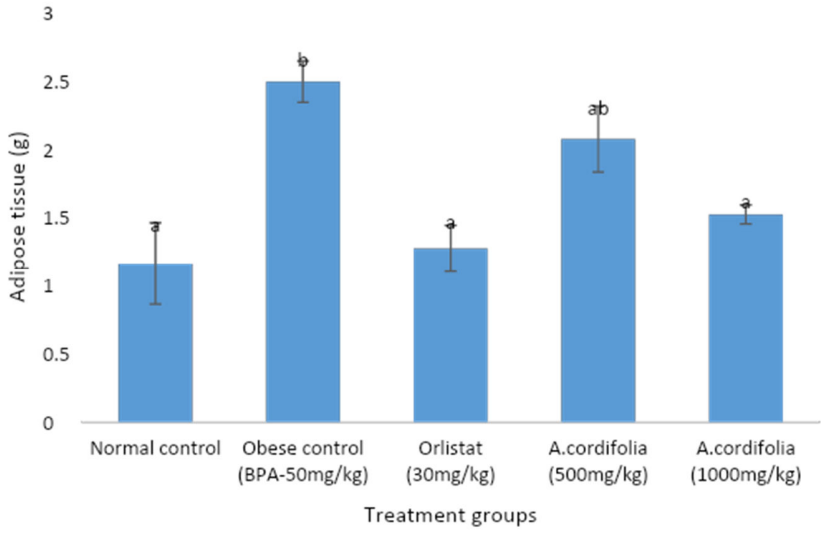

Figure 2. Effect of *A.cordifolia* treatment on adipose tissue of BPA induced obese Wistar rats.

Effect of *A. Cordifolia* Treatment on HMG-Coa Reductase Activity in HFD Induced Obese Wistar Rats

From the Result Obtained, The Tissue Mevalonic Acid Ratio (TMAR) was significantly ($p<0.05$) lower in the obese control (0.93±0.05) compared to the normal control (1.06±0.22). However, treatment with (1000mg/kg) of *A. cordifolia* showed the highest effect by significantly increasing the TMAR (1.41±0.18) compared to other treatment groups (15±0.29, 10±0.17). With regards to Magnitude of Cholesterol synthesis (MCS), the obese control showed slight difference compared to the normal control (50.31±8.36). Treatment with (1000mg/kg) of *A. cordifolia* significantly reduced the MCS (42.52±4.57) in comparison to other treatment groups

(56.05±5.55, 53.14±9.28). Furthermore, the percentage reduction of HMG-CoA reductase activity was significantly higher ($p<0.05$) in the obese control (50.99±2.23) showed when compared with the normal control (40.31±10.36). Moreover, the group treated with (1000mg/kg) *A. cordifolia* showed the most significant effect by greatly lowering (32.52±4.57) percentage reduction of HMG-CoA reductase activity thereby increasing HMG-CoA reductase activity. The result for the lipase activity showed a significant increase in the obese control (254.10±6.37) compared to the normal control (175.45±8.15). The treatment group that received 30mg/kg of orlistat

(197.63±5.84) and 1000mg/kg of *A. cordifolia* (201.67±5.84) showed a significant reduction in lipase activity when compared with obese group (254.10±6.37).

Table 3. Effect of *A. cordifolia* treatment on HMG-CoA reductase activity in BPA induced obese Wistar rats.

Groups	Treatment	TMAR	MCS (%g liver weight)	% reduction of HMG CoA activity	Lipase(U/L)
1	Normal control	$1.06±0.22^{a}$	$50.31±8.36^{a}$	$40.31±10.36^{a}$	$175.45±8.15^{a}$
2	Obese control	$0.93±0.05^{a}$	$60.99±2.23^{b}$	$50.99±2.23^{b}$	$254.10±6.37^{c}$
3	Orlistat (30mg/kg)	$1.15±0.29^{ab}$	$56.05±5.55^{b}$	$49.38±11.36^{b}$	$197.63±5.84^{a}$
4	*A.cordifolia* (500mg/kg)	$1.10±0.17^{ab}$	$53.14±9.28^{ab}$	$43.14±9.28^{ab}$	$242.00±9.88^{c}$
5	*A.cordifolia* (1000mg/kg)	$1.41±0.18^{b}$	$42.52±4.57^{a}$	$32.52±4.57^{a}$	$201.67±5.84^{b}$

Results are presented as Mean ±SEM. Means with same alphabets (such as a,a and b,b) are not significantly different; however, means with different alphabets (such as a,b and b,c) are significantly different $P<0.05$.

Effect of *A. Cordifolia* Treatment on Lipid Profile Parameters of Wistar Rats After BPA Administration

The effect of *A. cordifolia* treatment on Lipid profile parameters of Wistar rats after BPA-induced obese Wistar rats. The result shows that the obese control group had significantly higher levels of TC (263.89mg/dl ±8.05), TG (197.00mg/dl ±31.15), LDL-c (75.32mg/dl ±8.70), and VLDL-c (75.32mg/dl ±8.70), and lower levels of HDL-c (57.22mg/dl ±5.8) than the normal control group. However, treatment with *A.cordifolia* at both doses (500mg/kg and 1000mg/kg) resulted in significant reductions in TC (210.67mg/dl ±2.64, 173.33mg/dl ±39.91) and TG (170.70mg/dl ±21.05, 119.61mg/dl ±6.67) levels compared to the obese control group (263.89mg/dl ±8.05, 197.00mg/dl ±31.15). In addition, treatment with *A.cordifolia* at a dose of 1000mg/kg resulted in a significant increase in HDL-c (145.74mg/dl ±11.59) levels compared to the obese control group (57.22mg/dl ±5.81). With respect to LDL-c and VLDL-c, treatment with 500mg/kg and 1000mg/kg of *A.cordifolia* significantly lowered LDL-c (49.35mg/dl ±0.30, 10.50mg/dl ±1.24) and VLDL-c (25.60mg/dl ±5.53, 15.78mg/dl ±3.73) values in a dose dependent manner when compared with obese control (75.32mg/dl ±8.70, 45.09mg/dl ±9.52).

4. CONCLUSIONS

The study found that administering BPA induced obesity significantly increased the adipose tissue weight, liver weight, HMG CoA reductase and lipase activity, total cholesterol, triglycerides, low/very low-density lipoprotein levels, and decreased high-density lipoprotein levels of young male Wistar rats. However, treatment with ethanol extract of *A. cordifolia* was able to counteract these negative effects by significantly reducing the weight of adipose tissue and liver, as well as inhibiting HMG CoA reductase and lipase activity. Additionally, the extract was found to be effective in significantly decreasing total cholesterol, triglycerides, and low/very low-density lipoprotein levels and increasing high-density lipoprotein levels, proving its anti-hyperlipidemic effects in BPA-induced obesity. Furthermore, the presence of phenolics and flavonoids in the ethanol extract of *A. cordifolia* may enhance its ability to reduce adipose tissue and liver weight, inhibit HMG CoA reductase and lipase activity, thus exhibiting antihyperlipidemic activities.
Therefore, this study confirms the weight-reducing and antihyperlipidemic potential of *A. cordifolia*.

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