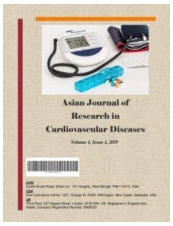

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Hypolipidemic Propensity of Ethanolic Extract of *Xylopia aethiopica* Fruit in Wistar Rats

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Authors' contributions

This work was carried out in collaboration among all authors. Author EOO conceptualized the study, Author PCU designed the study. Author INN managed the literature searches and managed the analyses of the study. Author UO wrote the protocol while author AIA performed the statistical analysis. All authors read and approved the final manuscript.

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ABSTRACT

Aim: This study is aimed at assessing the effect of Xylopia aethiopica fruit on the lipid profile of Wistar rats.
Methodology: The fruits of *Xylopia aethiopica* were obtained from new market in Aba, Abia State, Nigeria and were authenticated. They were air-dried and extracted using Soxhlet apparatus and ethanol as solvent. The median lethal dose (LD50) of the extract was determined using standard method. Thirty Wistar rats were used for this study. They were acclimatized for seven days, weighed and divided into five groups of six rats each. Animals in group A were administered 129.62 mg/kg body weight (10% of LD50) of *X. aethiopica* fruit extract, those in group B were administered 259.23 mg/kg body weight (20% of LD50) of *X. aethiopica* fruit extract, those in group C were administered 388.85 mg/kg body weight (30% of LD50) of *X. aethiopica* fruit extract, those in group D were administered 518.46 mg/kg body weight (40% of LD50) *of X. aethiopica* fruit extract, while those in group E (control) received normal feeds and water only. The administration was done once daily for

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28 days via oral route. At the end of 28 days treatment, animals were weighed and weights recorded, and were sacrificed under ether anaesthesia after an overnight fast. Lipid profile was determined using standard methods.

Results: The physical signs of toxicity observed in the animals included excitation, paw licking, increased respiratory rate, decreased motor activity, gasping and coma which was followed by death. A significant ($P<0.05$) reduction was in the total cholesterol, triglyceride, LDL-cholesterol, and VLDL-cholesterol concentrations of experimental animals when compared with those of the control group. However, a significant ($P<0.05$) increase was observed in the HDL-cholesterol and HDL/LDL ratio of experimental animals when compared with those of the control group.

Conclusion: The result of this study demonstrated that extract of *Xylopia aethiopica* fruit possesses hypolipidemic propensity and could be useful in the prevention and management of obesity and cardiovascular diseases. However, the extract could be toxic at dosage above 259.23 mg/kg body weight.

Keywords: Anti-obesity; cardiovascular disease remedy; hypolipidemic potential; xylopia aethiopicafruit.

1. INTRODUCTION

Lipids may be broadly defined as hydrophobic or amphiphilic small molecules; the amphiphilic nature of some lipids allows them to form structures such as vesicles, liposomes, or membranes in an aqueous environment [1]. Lipids are a large and diverse group of naturally occurring organic compounds that are related by their solubility in nonpolar organic solvents (e.g. ether, chloroform, acetone & benzene) and general insolubility in water [2]. They constitute a group of naturally occurring molecules that include fats, waxes, sterols, fat-soluble vitamins (such as vitamins A, D, E, and K), monoglycerides, diglycerides, triglycerides, phospholipids, etc. [3]. Although the term lipid is sometimes used as a synonym for fats, fats are a subgroup of lipids called triglycerides [4]. Lipids also encompass molecules such as fatty acids and their derivatives (including tri-, di-, monoglycerides, and phospholipids), as well as other sterol-containing metabolites such as cholesterol [5]. Although humans and other mammals use various biosynthetic pathways to synthesize and break down lipids, some essential lipids cannot be made this way and must be obtained from the diet [6]. Lipids have been reported to have several roles in the body [7].

Xylopia aethiopica Dunal (Annonaceae) is an aromatic plant commonly known as “African pepper”, “Ethiopia or Negro pepper”. It has been used in Europe, Asia and Africa as pepper substitute and spice in local cooking. In Nigeria, the common local names used in different languages to refer to this plant are: “Kimba” in Hausa, “Eeru” in Yoruba and “Uda” in Igbo [8]. Various parts of the plant have been traditionally employed in different therapeutic preparations. The mature fruits of green colour take a brown-black colouration after drying and are used as spices [9].

Fig. 1. *Xylopia aethiopica* fruit

Chemical components of *Xylopia aethiopica* have been helpful in the prevention and treatment of cancerous tumors. *Xylopia aethiopica* fruits contain alkaloids, flavonoids, terpenoids, fixed oil and volatile aromatic oil [10]. Key constituents are diterpenic and xylopic acids. *Xylopia aethiopica* oil contains carbohydrates and glycosides.

Xylopia aethiopica is known to have myriad chemical constituents with diverse therapeutic and pharmacological properties. These compounds, most of which have been isolated

and characterized, include saponins, sterols, carbohydrates, glycosides, mucilage, acidic compounds, tannins, balsams, cardiac glycosides, volatile aromatic oils, phenols [11], alkaloids, rutin and fixed oils. The plant also contains vitamins A, B, C, D, and E, and proteins together with high amounts of minerals like copper, manganese and zinc [11]. *X. aethiopica* has been reported to contain hypoglycemic agents [12]. This study is therefore aimed at assessing its effect on lipid profile of Wistar rats.

2. MATERIALS AND METHODS

2.1 Collection and Authentication of Plant Materials

The fruits of *Xylopia aethiopica* were obtained from new market in Aba, Abia State and were identified and authenticated by Prof. (Mrs) Margaret Bassey of the Department of Botany and Ecological Studies, University of Uyo with the voucher number UU/PH/4e. The plant was deposited in the Herbarium of the Department of Pharmacognosy and Natural Medicine, University of Uyo, Akwa-Ibom State, Nigeria.

2.2 Extraction of Plant Materials

The extraction was carried out in the Post-graduate Laboratory of Department of Pharmacognosy and Natural Medicine, Faculty of Pharmacy, University of Uyo, Akwa-Ibom State, Nigeria. It was carried out according to the method described by Ogbuagu et al. [10]. The fruits were washed under running tap water to remove contaminant and air-dried. This plant material was then pulverized using laboratory blender to provide a greater surface area. The pulverized plant material was macerated in 250 mL of 99.8% ethanol (Sigma Aldrich) contained in round bottom flask, which was then attached to a Soxhlet extractor coupled with condenser and heating mantle (Isomantle). It was then loaded into the thimble, which is placed inside the Soxhlet extractor. The side arm is lagged with glass wool. The mixture was heated using the heating mantle (Isomantle) at 60°C and as the temperature increases it begins to evaporate, moving through the apparatus to the condenser. The condensate then drips into the reservoir containing the thimble. Once the level of solvent reaches the siphon it pours back into the flask and the cycle begins again. This continues until it is exhaustively extracted. The process runs for a total of 13 hours. Once it was set up, it was left to run without interruption as long as water and power supply were not interrupted. The equipment was turned on and off and overnight running was not permitted, and the time split over a number of days. The extract was poured into 1000 mL beaker and concentrated to dryness in water bath (A3672- Graffin Student Water Bath) at 35°C. The total weight of the marc (residue) and the concentrated extract were recorded, these processes took several days. The dried extract was preserved in the refrigerator at 4°C for further analysis.

2.3 Determination of Median Lethal Dose (LD_{50})

The median lethal dose (LD_{50}) of the extract was estimated using albino mice according to the method described by Airaodion et al. [13]. This method involves two phases:

In phase one, five groups containing five mice each weighing between 20 g and 27g were fasted for 18 hours. They were respectively administered 1000 mg/kg, 2000 mg/kg, 3000 mg/kg, 4000 mg/kg and 5000 mg/kg body weight intraperitoneally (i.p) and were observed for physical signs of toxicity and mortality for 24 hours. 1000 mg/kg recorded 0% mortality while 2000 mg/kg, 3000 mg/kg 4000 mg/kg and 5000 mg/kg recorded 100% mortality within 24 hours. Based on the value of phase one, phase two was conducted.

In phase two, twenty albino mice weighing between 20 – 27 g were grouped into four of five mice per group and were fasted for 18 hours. Each group was administered 1200 mg/kg, 1400 mg/kg 1600 mg/kg and 1800 mg/kg body weight intraperitoneally (i.p) and was observed for physical signs of toxicity and mortality within 24 hours. 1200 mg/kg recorded 0% mortality while 1400 mg/kg, 1600 mg/kg and 1800 mg/kg recorded 100% mortality within 24 hours. The LD_{50} was calculated as geometrical means of the maximum dose producing 0% (a) and the minimum dose producing 100% mortality (b).

$$LD_{50} = \sqrt{ab}$$

2.4 Experimental Design

Thirty Wistar rats obtained from the University of Uyo, Nigeria were used for this study. They were acclimatized for seven days before the commencement of the experiment. They were weighed and divided into five groups of six rats

each. Groups A, B, C, D served as the experimental groups, while group E served as the control. Animals in group A were administered 129.62 mg/kg body weight (10% of LD_{50}) of *X. aethiopica* fruit extract, those in group B were administered 259.23 mg/kg body weight (20% of LD_{50}) of *X. aethiopica* fruit extract, those in group C were administered 388.85 mg/kg body weight (30% of LD_{50}) of *X. aethiopica* fruit extract, those in group D were administered 518.46 mg/kg body weight (40% of LD_{50}) of *X. aethiopica* fruit extract, while those in group E (control) received normal feeds and water only. The administration was done once daily for 28 days via oral route. At the end of 28 days treatment, animals were weighed and recorded, and were sacrificed under ether anaesthesia in a desiccator after an overnight fast. Blood samples were collected via cardiac puncture.

2.5 Determination of Lipids

Lipids were extracted and determined according to previously described methods [14,15].

2.6 Statistical Analysis

Results are expressed as mean ± standard deviation. The levels of homogeneity among the groups were assessed using One-way Analysis of Variance (ANOVA) followed by Tukey's test. All analyses were done using Graph Pad Prism Software Version 5.00 and P values < 0.05 were considered statistically significant.

3. RESULTS

The physical signs of toxicity observed in the animals included excitation, paw licking, increased respiratory rate, decreased motor activity, gasping and coma which was followed by death. In the first phase of the median lethal dose determination, no mortality was recorded in the group treated with 1000 mg/kg body weight of *X. aethiopica* fruit extract. However, 100% mortality was recorded in the groups treated with 2000, 3000, 4000, and 5000 mg/kg body weight of *X. aethiopica* fruit extract respectively. Similarly, in the second phase of medial lethal dose determination, no mortality was recorded in the group treated with 1200 mg/kg body weight of *X. aethiopica* fruit extract while 100% mortality was recorded in the groups treated with 1400, 1600, and 1800 mg/kg body weight of *X. aethiopica* fruit extract respectively as presented in Table 1.

The median lethal dose (LD_{50}) was calculated as geometrical means of the maximum dose producing 0% (a) and the minimum dose producing 100% mortality (b).

$$LD_{50} = \sqrt{ab}$$

Where a = 1200 mg/kg

b = 1400 mg/kg

LD_{50}= 1296.15 mg/kg

In this study, ethanolic extract of *X. aethiopica* fruit was observed to elicit hypolipidemic effect on experimental animals when compared with those of the control group as presented in Figs 2-7. A significant ($P<0.05$) reduction was in the total cholesterol, triglyceride, LDL-cholesterol, and VLDL-cholesterol concentrations of experimental animals when compared with those of the control group. However, a significant ($P<0.05$) increase was observed in the HDL-cholesterol and HDL/LDL ratio of experimental animals when compared with those of the control group.

Table 1. The median lethal dose (LD_{50}) of *Xylopia aethiopica* fruit extract

Study Phase/ (Animal)	Dosage of Extract (mg/kg) b.w	No of Mice per Group	No. of Death Recorded	% Mortality
PHASE ONE				
I	1000	5	0	0
II	2000	5	5	100
III	3000	5	5	100
IV	4000	5	5	100
V	5000	5	5	100
PHASE TWO				
I	1200	5	0	0
II	1400	5	5	100
III	1600	5	5	100
IV	1800	5	5	100

LD_{50}= 1296.15 mg/kg

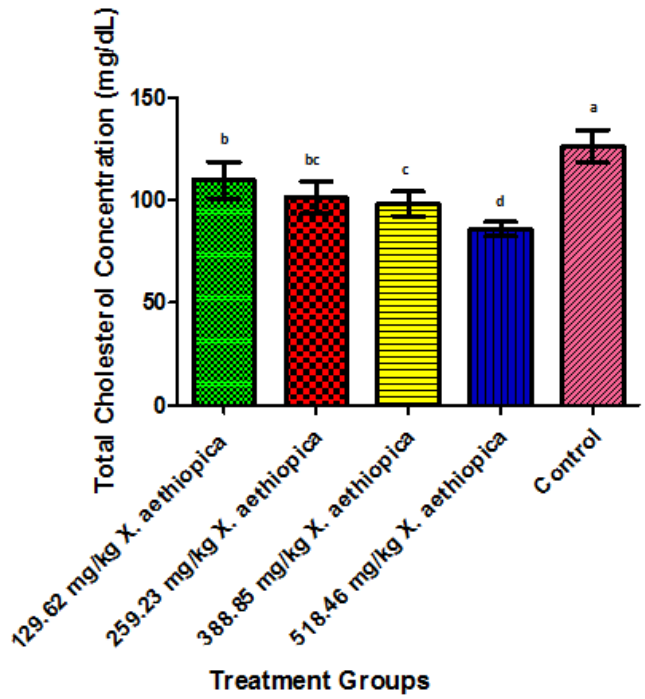

Fig. 2. Effect of *Xylopia aethiopica* fruit extracton the Concentration of Total Cholesterol of Animals after 28 days of Treatment

Results are presented as mean ± SD with n = 6. Bars with different letters are significantly different at P<0.05

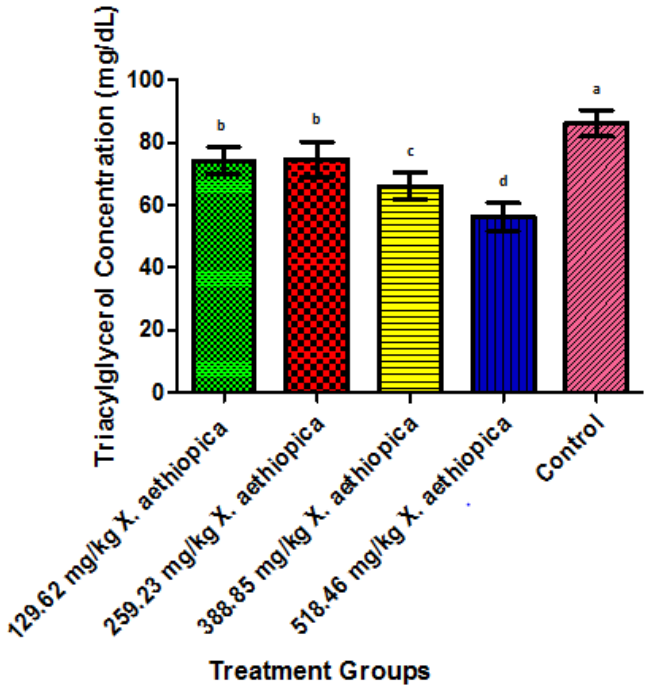

Fig. 3. Effect of *Xylopia aethiopica* fruit extracton the Concentration of Triacylglycerol of Animals after 28 days of Treatment

Results are presented as mean ± SD with n = 6. Bars with different letters are significantly different at P<0.05

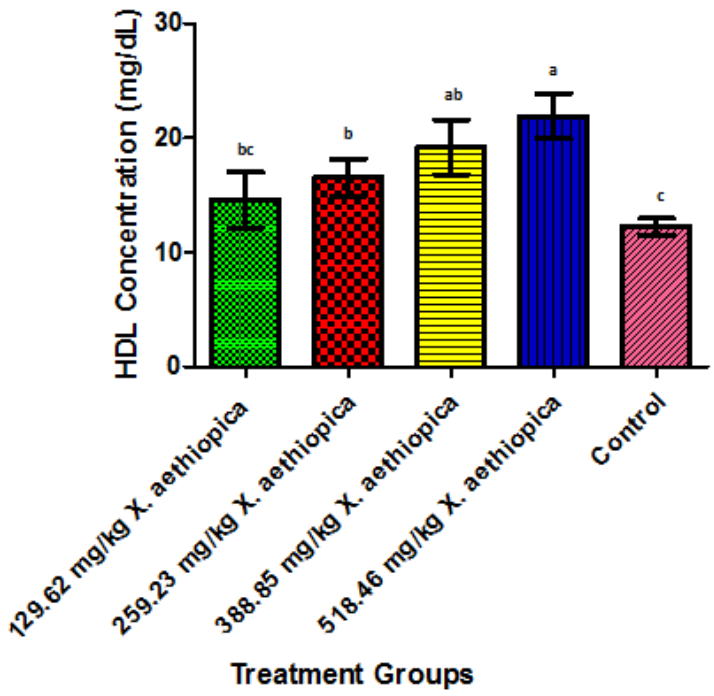

Fig. 4. Effect of *Xylopia aethiopica* fruit extracton the Concentration of High Density Lipoprotein (HDL) Cholesterol of Animals after 28 days of Treatment

Results are presented as mean ± SD with n = 6. Bars with different letters are significantly different at P<0.05

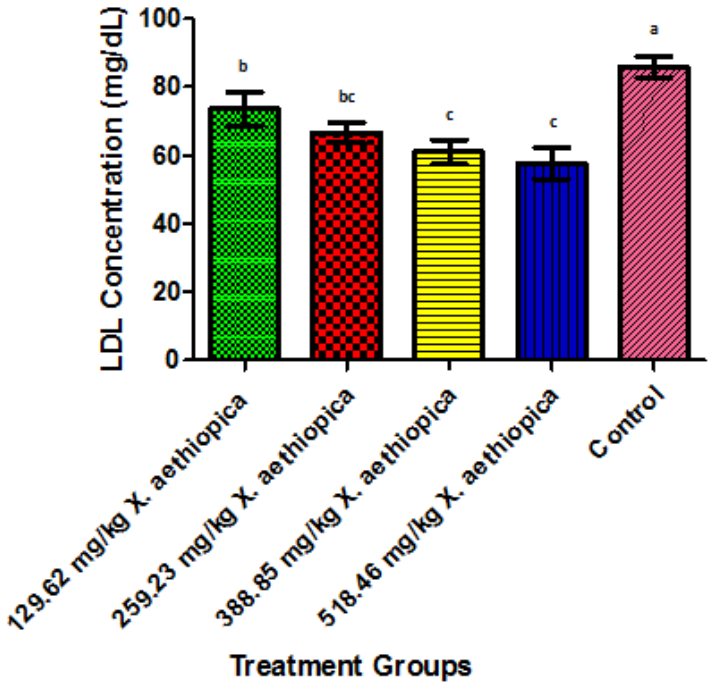

Fig. 5. Effect of *Xylopia aethiopica* fruit extracton the Concentration of Low Density Lipoprotein (LDL) Cholesterol of Animals after 28 days of Treatment

Results are presented as mean ± SD with n = 6. Bars with different letters are significantly different at P<0.05

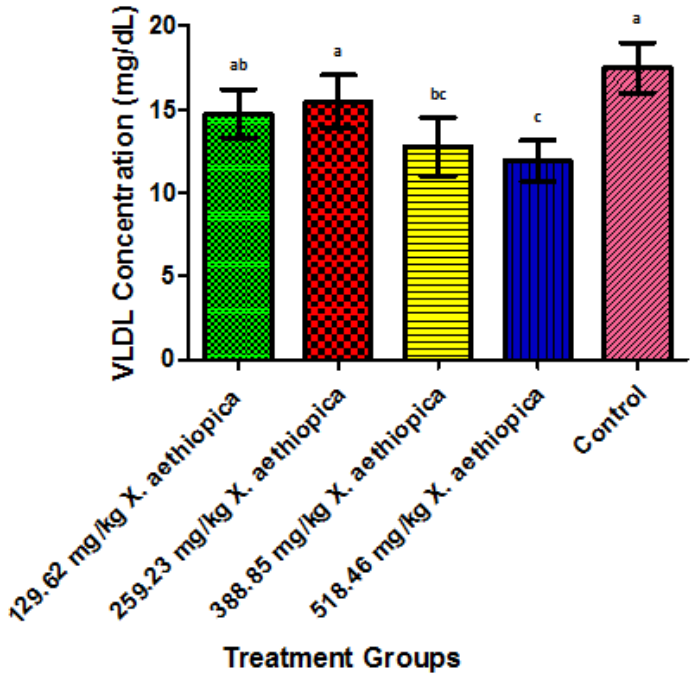

Fig. 6. Effect of *Xylopia aethiopica* fruit extracton the Concentration of Very Low Density Lipoprotein (VLDL) Cholesterol of Animals after 28 days of Treatment

Results are presented as mean ± SD with n = 6. Bars with different letters are significantly different at P<0.05

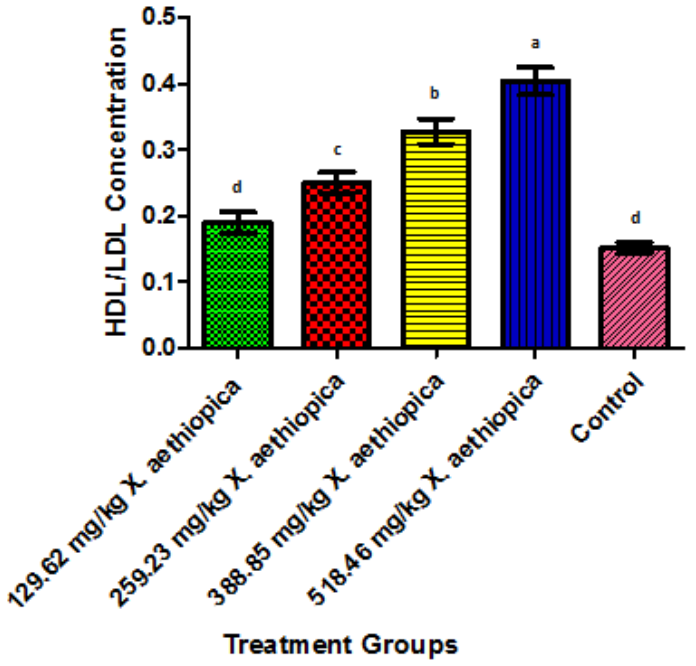

Fig. 7. Effect of *Xylopia aethiopica* fruit extracton the Concentration of HDL/LDL-Cholesterol Ratio of Animals after 28 days of Treatment

Results are presented as mean ± SD with n = 6. Bars with different letters are significantly different at P<0.05

4. DISCUSSION

The acute toxicity study of the plant extracts recorded 100% mortality at a dose of 1200 mg/kg bodyweight and above as presented in table 1. This shows that the fruit of *X. aethiopica* is highly toxic. The physical signs of toxicity observed in the animals included excitation, paw licking, increased respiratory rate, decreased motor activity, gasping and coma which was followed by death.

Fruits of *X. aethiopica* have been reported to have hypolipidemic properties [12]. Apart from the regulation of carbohydrate metabolism, insulin plays an important role in lipid metabolism. Insulin insufficiency, as in diabetes mellitus, is associated with hypercholesterolemia and hypertriglyceridemia, which have been reported to occur in experimental diabetic rats [16]. Hypercholesterolemia could result in a relative molecular ordering of the residual phospholipids, resulting in a decrease in membrane fluidity [17]. Accumulation of triglycerides is one of the leading risk factors in coronary heart disease (CHD). Lipid and lipoprotein abnormalities have been shown to play a major role in the pathogenesis and progression of several disease conditions [18].

In this study, total cholesterol and triglycerides concentrations were observed to decrease significantly when animals treated with *Xylopia aethiopica* fruit extract were compared with those of the control group at $P<0.05$ (Figs. 2 and 3). This corresponds to the study of Orji et al. (2016) who reported the sub-acute toxicity and hypolipidaemic effect of aqueous and methanol fruit extract of *Xylopia aethiopica*. This could mean that *Xylopia aethiopica* fruit extract has the potential to prevent the progression of Coronary Heart Disease (CHD). Despite the availability of known anti-diabetic medications, remedies from medicinal plants are used with increasing success to treat this disease and manage its complications better [19]. Furthermore, it has been suggested that plant drugs and herbal formulations are less toxic and are free from side-effects compared with synthetic drugs, leading to an increasing preference for traditional plants over synthetic drugs [20,21]. Increased evidence of therapeutic effectiveness of herbal medicines may have influenced the interest of world health organization (WHO) in hypoglycemic agents of plant origin used in the traditional treatment of diabetes [22]. This result is also in agreement with the findings of Nnodim et al. [23], who reported a significant decrease in plasma cholesterol, triglyceride and LDL cholesterol when compared with the control after 14 days treatment with *Xylopia aethiopica* fruit extract. However, the result of the present study is in contrast with the findings of Abaidoo *et al*. [11], who reported a significant increase in total cholesterol and triglyceride of animals treated with *Xylopia aethiopica* fruit extract. Hypertriglyceridaemia has been reported in diabetic animals [24]. This was reported to be due to increased absorption and formation of triglycerides in the form of chylomicrons following exogenous consumption of diet rich in fat or through increased endogenous production of triglyceride-enriched hepatic VLDL-cholesterol and decreased triglyceride uptake in peripheral tissues [14]. Hypercholesterolaemia has also been reported in diabetic animals [25].This was attributed to the increased dietary cholesterol absorption from the small intestine following the intake of high fat diet in a diabetic condition. However, the levels of serum triglyceride, VLDL-cholesterol and total cholesterol were significantly reduced in animals treated with fruit extracts of *Xylopia aethiopica* when compared with those of the control group in the present study. Moreover, it can be conjectured that the lipid lowering effects of *Xylopia aethiopica fruit extract* could be due to the inhibition of hepatic cholesterol, triglyceride and possibly fatty acid synthesis by the phenolic constituents of *Xylopia aethiopica fruit extract* reported by Ogbuagu et al. [10].

Hypertriglyceridaemia has also been reported to be a predictor of hypertension risk [26]. In the peripheral vascular system, endothelial cells rely on lipoproteins for the transfer of neutral sterols at this site. Although free cholesterol is transferred to HDL-cholesterol particles through the functioning of a designated HDL-cholesterol receptor, lecithin cholesterol acyl transferase (LCAT) serves to maintain the concentration toward the HDL core and preserve the hydrophobic nature that facilitates the transfer. Esterification of cholesterol produces cholesterol ester (CE), which is concentrated in HDL core, and may be transferred by cholesterol ester transfer protein (CETP) in the plasma compartment to apo-B containing lipoproteins in exchange for triglyceride. Increased CETP activity would suggest an enrichment of apo-B lipoproteins in plasma, while simultaneously decreasing HDL-cholesterol, and has generally been considered pro-atherogenic [27]. This probably explains why *Xylopia aethiopica fruit*

extract may lead to a reduction in the risk of developing heart diseases since a high HDL-cholesterol/LDL-cholesterol ratio has been shown to be beneficial and is indicative of a lower risk of cardiovascular diseases [16].

HDL-cholesterol and LDL-cholesterol are two of the four main groups of plasma lipoproteins that are involved in lipid metabolism and the exchange of cholesterol, cholesterol ester and triglycerides between tissues [28]. Numerous population studies have shown an inverse correlation between plasma HDL-cholesterol levels and risk of cardiovascular disease, implying that factors associated with HDL-cholesterol protect against atherosclerosis. Some of these factors appear to have antioxidant and anti-inflammatory effects which may obviate processes that initiate atherogenesis [15,19].

Epidemiological studies have also shown that elevated concentrations of total cholesterol and/or LDL-cholesterol in the blood are powerful risk factors for coronary heart disease [17,29]. Most extra-hepatic tissues, although having a requirement for cholesterol, have low activity of the cholesterol biosynthetic pathway. Their cholesterol requirements are supplied by LDL, which is internalized by receptor-mediated endocytosis. A major function of HDL-cholesterol is to enhance reverse cholesterol transport by scavenging excess cholesterol from peripheral tissues followed by esterification through lecithin: cholesterolacyltransferase and delivering it to the liver and steroidogenic organs for subsequent synthesis of bile acids and lipoproteins and eventual elimination from the body. This role of HDL-cholesterol has been shown to be responsible for its atheroprotective properties. HDL-cholesterol also regulates the exchange of proteins and lipids between various lipoproteins [19,26].

In addition, HDL-cholesterol provides the protein components required to activate lipoprotein lipase which releases fatty acids that can be oxidized by the ß-oxidation pathway to release energy [14]. Most importantly, HDL-cholesterol can inhibit oxidation of LDL-cholesterol as well as the atherogenic effects of oxidized LDL-cholesterol by virtue of its antioxidant property [30]. LDL is a lipoprotein that transports cholesterol and triglyceride from the liver to peripheral tissues. It enables fat and cholesterol to move within the water-blood solution of the blood stream. LDL is often called bad cholesterol; hence low levels are beneficial [27].

Interestingly, the administration of *Xylopia aethiopica* fruit extract for *28 days* in this study caused a significant increase in the serum level of HDL-cholesterol when compared with the control animals at $P<0.05$. This is in agreement with the findings of Nnodim *et* al. [23], who reported a significant increase in HDL cholesterol in animals treated with *Xylopia aethiopica fruit extract but contradicts the findings of* Abaidoo et al. [31], who reported a significant decrease in HDL cholesterol of animals treated with *Xylopia aethiopica* fruit extract. HDL-cholesterol is usually referred to as the 'good cholesterol' [27]. Again, *Xylopia aethiopica* fruit extract administration significantly decreased the concentration of LDL-cholesterol (bad cholesterol) when compared with that of the control group at $P<0.05$.The combined effect of increased HDL-cholesterol (good cholesterol) and decreased LDL-cholesterol (bad cholesterol) in the present study resulted in an increased HDL-cholesterol/LDL-cholesterol ratio in animals treated with *Xylopia aethiopica* fruit extract when compared with the control group at $P<0.05$. This strongly supports the notion that dietary supplementation with the extract of some medicinal plants may lead to a reduction in the risk of developing heart diseases, because a high HDL-cholesterol/LDL-cholesterol ratio has been shown to be beneficial and is indicative of a lower risk of CHD [32]. In fact, the mechanism leading to lipid alterations in *Xylopia aethiopica* treated rats could be that there is reduction in stimulation of sympathetic adrenal system leading to decreased secretion of catecholamine resulting in decreased concentration of plasma free fatty acids which might further result in decreased secretion of hepatic free fatty acids [33]. Hence, the decreased level of total cholesterol, triglyceride and LDL-cholesterol.

The decreases in lipids observed in this study might also be mediated via the documented *Xylopia aethiopica*-induced inhibition of dietary lipid absorption in the gastrointestinal tract, which is thought to be achieved via the reduction in the bile salts which are required for cholesterol absorption in the small intestine. The observed effects of dietary *Xylopia aethiopica* on lipid concentrations in this study are similar to those reported by Nwafor [34], who observed that extracts of *Xylopia aethiopica* demonstrated a dose-dependent reduction in serum total cholesterol, triglyceride and LDL-cholesterol levels, but caused increases in levels of high density lipoprotein cholesterol.

In fact, Xylopic acid (an acid derived from *Xylopia aethiopica*) has been identified to decrease serum total cholesterol while increasing HDL-cholesterol. The activity of the *Xylopia aethiopica* extract in decreasing both total cholesterol and LDL-cholesterol was earlier reported by Woode et al. [35]. LDL molecules are the major transporters of cholesterol in the bloodstream and are considered ‘‘bad cholesterol’’ because they carry fats out of the liver to the blood vessels and seem to encourage the deposition of cholesterol in the arteries. The observed significant decrease in LDL, TC and triacylglycerol, which in essence increased HDL level, signifies that *Xylopia aethiopica* is a potential hypolipidemic agent and may further explain its popular addition in herbal remedies for diabetes mellitus, and in hypolipidemic therapies.

5. CONCLUSION

The result of this study demonstrated that extract of *Xylopia aethiopica* fruit possesses hypolipidemic propensity and could be useful in the prevention and management of obesity and cardiovascular diseases. However, the extract could be toxic at dosage above 259.23 mg/kg body weight.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Animal ethic Committee approval has been collected and preserved by the author.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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