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Effect of *Tetracarpidium Conophorum* Nut Extract on Lipid Profile of Monosodium Glutamate Induced Obesity in Wistar Rats

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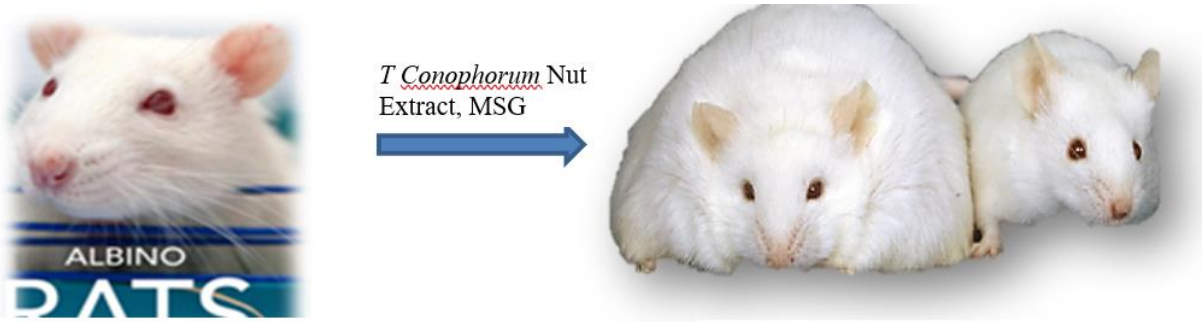
Abstract

Obesity is a popular health problem in the world, characterized by metabolic disorder such as Arteriosclerosis, Hyperlipidemia, Type 2 Diabetes mellitus and cardiovascular disease. This study is carried out to determine the effect of *Tetracarpidium conophorum* nut extract on serum lipid profile of Monosodium Glutamate induced Obesity in rats. Twenty five (25) rats, 15 females and 10 males were obtained from the animal house of the Department of Biochemistry, University of Calabar. The animals were divided and cohabited in five well ventilated cages in the ratio of 3:2 females to males respectively. Obesity was induced in the pups by intravenous administration 4mg/kg body weight of MSG on day 2, 4, 6, 8 and 10. The animals were confirmed Obese using their BMI after 12 weeks. The result of the analysis shows that there was no significant changes ($P>0.05$) in the lipid profile of the Obese animals (Obsc) relative to the normal (NC). Equally the Obsc group did not show any significant ($P<0.05$) change relative to the Obc. However, TC, HDL-C, LDL-C decreases and VLDL-C, HDL: TC and LDL: HDL ratios of Obsc increases relative to Obsc group, also the changes were insignificant ($P<0.05$) upon treatment with the different fractions of the *Tetracarpidium conophorum* nuts, though EWE treated group shows decrease in total Cholesterol, Triglycerols, LDL-C and VLDL-C while HDL-C decrease relative to Obsc. This Study shows that *Tetracarpidium Conophorum* have the ability to down regulate Serum lipids.

Keywords: *Obesity; BM1; Wistar Rats; Monosodium Glutamate; Orlistat; Tetracarpidium Conophorum; Lipid Profile*

Graphical Abstract

Tetracarpidium Conophorum Nut Extract on obesity in Wistar Rats, the central image visually captures the journey from a normal state to an obese state resulting from exposure to the extracts.The extracts bioactive compounds play a crucial role in this transformation, as the rats were confirmed Obese using their BMI after 12 weeks. The figure below shows the transformation in the rats before and after treatment.



Wistar Albino Rats before Treatment

Obese Wister Rats after treatment

1. Introduction

Obesity, also called Corpulence **or** fatness, is the excessive accumulation of Body fat usually caused by the consumption of more calories than the body can use[1]. Obesity is considered a principal public health concern and ranked as the fifth foremost reason for death globally. Overweight and obesity are one of the main lifestyle illnesses that leads to further health concerns and contributes to numerous chronic diseases, including Cancers, Diabetes, Metabolic syndrome, and Cardiovascular diseases[2]. It is most often defined by the body mass index (BMI), a mathematical formula of weight-for-height index. Body Mass Index is defined as the subjects weight divided by the square of their height and calculated as follows; BMI = mh^2 Where m and h are the subject's weight and height respectively.The World Health Organization also predicted that 30% of death in the world will be initiated with lifestyle diseases in 2030 and can be stopped through the suitable identification and addressing of associated risk factors and behavioral involvement policies[4].Studies have discussed the relationships between genetics, epigenetics and environment in Obesity and explored the roles of epigenetic factors in metabolism regulation and obesity risk as well as its complications[5-6].

Roh and Jung used the porcine pancreatic lipase assay (PPL; triacylglycerol lipase, EC 3.1 .1 .3) in vitro activity to screen crude extracts from 400 plants for their anti-obesity activity. 44 plant extracts out of the 400 species of plants analyzed, using the substrate 2,4-dinitrophenylbutyrate in a porcine pancreatic lipase assay, demonstrated strong anti-lipase activity[7]. Researchers have also noted that various forms of obesity, including Abdominal Obesity, are related to increased risk of several chronic conditions and diseases, which include Asthma, Cancer, Diabetes, Hypercholesterolemia, and Cardiovascular diseases[8-9]. Thus, while Obesity is undoubtedly a condition, it also exacerbates pre-existing conditions and instigates new ones[10]. More specifically, Bischoff et al maintained that obesity can affect nearly every organ system, from the cardiovascular (CV) system to the Endocrine system,Central Nervous system, and the gastrointestinal (GI) system[11]. In addition, Obesity is associated with the growing prevalence of several CV conditions, from Hypertension and Coronary heart disease (CHD) to atrial fibrillation (AF) and even total heart failure[12].

Different drugs have been developed for the management and treatment of Obesity, among includes Orlistat and Sibatramine. Sibatramine was withdrawn from distribution by the European Union countries in 2010, because of increase in risk of cardiovascular events,

leaving just Orlistat as the presently known drug for obesity in the market[13]. On June 4, 2021, the FDA announced the long-anticipated approval of Wegovy, an injectable medication taken once per week for weight management[14]. Over the years, many other classes of Anti-Obesity drugs have been developed including (1) Lorcaserin (2) Phentermine (3) Bupropion (4) Liraglutide. These drugs have serious side effects like Oily spotting, fecal incontinence and fecal urgency and the possibility of serious liver injury[15]. These research work evaluated and carried out a study on the effect of *Tetracarpidium conophorum* on monosodium glutatamate induced obese rat with interest in lipid profile including total cholesterol (TC), triacylglycerol (TG), high density lipoprotein (HDL) cholesterol, low density lipoprotein (HDL)cholesterol, and very low density lipoprotein (VLDL) cholesterol. Monosodium glutamate (MSG) is the world's most extensively used food additive and is generally recognized as safe according to the FDA. Further, it is reported that MSG comprises two isomers, i.e., L-glutamate and D glutamate enantiomers, but only L-glutamate enantiomer is responsible for enhancing the flavor [16]. Administration of MSG induces toxic effect in various region of the brain,thymus, liver and kidney. MSG is not a true allergen but may directly affect immune response by stimulating or damaging the nervous system. MSG also induces obesity[17]. This molecule was identified about one hundred years ago by Kikunae Ikeda as the fifth basic taste, in addition to sweet, sour, salty, and bitter. MSG is found in high-protein food products, such as meat or fish, and in certain types of cheese (Roquefort and Parmesan) or Vegetables (tomatoes, mushrooms, broccoli)[18].

Orlistat is a drug designed to treat Obesity. Orlistat has been shown to reduce serum total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels independent of weight loss. In line with previous studies, our clinical trial showed that concomitant administration of orlistat and phentermine significantly decreases total cholesterol and non-high-density lipoprotein cholesterol (non-HDL-C) and improves vascular endothelial cell function compared with phentermine alone. Therefore, orlistat might decrease CVD risk. Nevertheless, the exact mechanism involved in the previous results is unclear, and further research is needed to evaluate the drug's long-term benefit on cardiovascular risk[19-20]. Orlistat works by inhibiting gastric and pancreatic lipases, the enzymes that breaks down triglycerides in the intestine[21]. *Tetracarpidium conophorum* is a climbing shrub 1 0-20ft long. In Nigeria, it is predominant in the south where it is called by the Igbos as Ukpa, Awusa or Asala by Yorubas, Okwe in Edo, Gwandi bairi in Hausa.It is a woody peremial climber that belongs to the family Euphorbiacea, it is commonly called African Walnut and It's found in the forest

regions of Africa and India. In Nigeria, it is found in Abak, Uyo, Etinan, Akamkpa, Akpabuyo, Lagos and Ibadan[22].The amino acids component present in *Tetracarpidium conophorum* includes Glutamic acid (13mg/g) which has the highest Amino acid and Leusine 0.32mg/g which has the lowest essential amino. Walnuts are a rich source of nutrients and bioactive phytochemicals. Large amount of Polyunsaturated Fatty Acids in walnuts including Linoleic acid (LA) and α-Linoleic acid (ALA) have been shown to enhance brain, health and function.[23]

This research work evaluated and carried out a study on the effect of Tetracarpidium conophorum on monosodium glutatamate induced Obese rat with interest in lipid profile including total cholesterol (TC), triacylglycerol (TG), high density lipoprotein (HDL)cholesterol, low density lipoprotein (HDL) cholesterol, and very low density lipoprotein (VLDL) cholesterol**.**Tetracarpidium conophorum in experimental animal (albino wistar rats) in regards to lipid profile shows that there was no significant effect on the lipid profile of the obese animals (obc) administered African walnut extract over the 6- weeks period.

2. Materials and Methods

2.1 Experimental Animals

25 albino rats, 15 females and 10 males were obtained from the animal house of the Department of Biochemistry, University of Calabar. The animals were divided and co-habited in five well ventilated cages in the ratio of 3:2 females to males respectively and fed with normal poultry feeds specifically growers after three days of acclimatization. Their secondary sex organs were observed when they are beginning to get viable to avoid mating and pregnancy. The neonates were fed with normal poultry feeds (vital grower) and were allowed to grow, weighing up to 140 and ≥150 g. The pregnant animals were monitored closely for isolation when they are close to parturition.

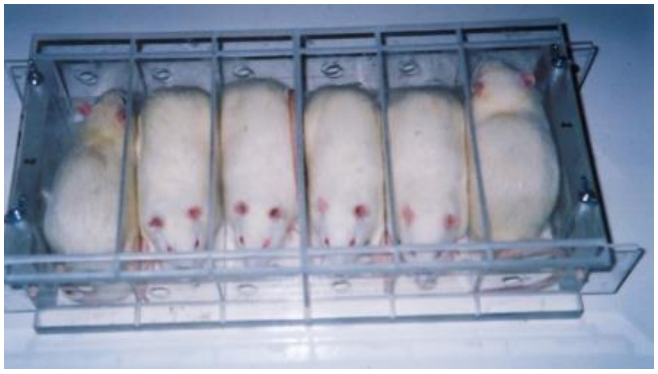


Figure 1: Experimental animals used in this study.

2.2 Induction of Obesity in the Neonates

Pups produced by the co-habited animals were induced with obesity at 2 days old using monosodium glutamate (MSG) according to the methods used earlier by Alarcon-Aguilar et al, (2008). Each animal was injected a single dose of 4 mg/kg body weight of MSG reconstituted in normal saline, through intraperitoneal route once a day, and the induction started on postnatal day 2 and spanned through day 4, 6, 8 and10 to produce the obese models. Another group of the pups from the co-habited rats were separately injected with an equimolar volume of normal saline while they were yet breastfeeding. The pups were all together weaned immediately they start picking up food and that lasted for three week of postnatal life, while the animals were kept under close observation to ensure immediate isolation or separation once. The materials used in this project includes an electronic weighing balance, hand gloves, facemask, sterile syringes, dissecting sets, cotton wool, saw dust, water, EDTA sample bottle, cages, MSG, Enamel stainless plate, vital grower feed.

Figure 2: Induction of Obesity in Neonates**.**

2.3 Collection and Preparation of Sample

The Fresh Tetracarpidium conophorum (African walnut) was bought from Okuni in Ikom Local Government of Cross River State and was conveyed to Calabar in black polythene bags. The walnuts were de-shelled and the edible seeds chopped into chips and sun dried. After which the sample was blended into coarse granules (semi-powdered form) with a clean manual blender. The blended sample was weighed and then extracted in 80% ethanol, and finally ethyl acetate to obtained two fractions (the ethanol whole extract and the ethyl acetate extract) and the ethanol residue. The fractions were collected and concentrated in rotary evaporator at 50 ℃ to 10%, and then allowed in an oven (55℃) for complete evaporation to yield the final fractions for each solvent.

2.4 Experimental Design

The obesity-induced animals were randomly divided into five (5) experimental group according to their weights with each containing at least 7 animals per group. While the non-induced animals, form the normal control group as shown in Table below.

Table 1. Distribution of animals into experimental groups

S/N	GROUPS	NO OF ANIMALS	TREATMENT
1	NC	7	Normal Saline
2	OBC	7	Normal Saline
3	OBSC	7	Standard Anti Obesity drug (Orlistat) 5.14 mg/kg b.w.
4	OB-EWE	7	Whole extract of T. conophorum (2 g/kg b.w)
5	OB-EAE (RESIDUE)	7	Ethyl acetate extract of T.conophorum (2 g/kg b.w)
6	OB-ER (RESIDUE)	7	Ethanol extract of T.conophorum (2 g/kg b.w)

NC = Normal Control

OBC = Obese control

OBSC = Obese standard control

EWE = Ethanol whole extract

EAE = Ethyl acetate extract

ER = Ethanol extract residue

The ethanol whole and ethyl acetate extracts came out in oily form and were administered directly in calculated doses of 2 g/kg body weight once a day to the animals in group IV and V respectively by oral gavages for 6 weeks. While in group VI, the obese animals were treated with 2 g/kg body weight of the ethanol residue reconstituted in normal saline. Also the animal in group I and II were treated with equimolar volume of normal saline and 5.14 mg/kg body weight of Orlistat (standard Anti-Obesity drug) respectively. The weight (g), nasal-anal length (cm) and waist circumference (cm) of the animals were taken fourth nightly and then random blood sugar was taken every two weeks.

2.5 Collection of samples for blood serum analysis

After six weeks of treatment and overnight fasting of the animals, they were all euthanized using 2 μL of ketamine per gram body weight of animals. The animals were dissected, and blood samples collected by cardiac puncture. The blood collected from each rat was divided into two fractions; one portion was collected into a labelled heparinized sample tube, for hematological analysis, while the second portion was collected into plain sample tubes with screwcap for serum separation. The blood samples in the plain tubes were allowed to coagulate and then the serum was separated using Pasteur's pipette after spinning in a MSE tabletop centrifuge for 10 minutes and the sera was stored in a refrigerator at 4℃ until required for use. While the heparinized blood was immediately used for hematological analysis within 24 hours.

2.6 Assay of serum lipid profile

Assay of Total cholesterol (TC): The serum TC concentration was estimated using Randox assay kit (CHOD-PAP method). Principle: This method is based on the release of free cholesterol from ester form by enzymatic hydrolysis, and thereafter become oxidized to form hydrogen peroxide (H_2O_2) as a by-product. The H_2O_2 formed is quantified via a Quinoneimine indicator, which is formed from the reaction between H_2O_2 and 4-Aminoatipyrene in the presence of phenol and peroxide. Generally, the concentration of H_2O_2 formed is proportional to the initial concentration of cholesterol in the sample. It can be calculated by the equation given as Total cholesterol = LDL+HDL+Triglyceride/5

2.7 Assay of Serum Triacylglycerol (TG) concentration:

The total serum Triacylglycerol concentration was estimated by enzymatic test of GPO-PAP method, described by the manual contained in Randox reagent kits. Principle: The principle of this method involves lipase enzyme hydrolysis of triacylglycerol to yield glycerol and free fatty acids. The glycerol formed is then phosphorylatedby glycerol kinase (GK) to glycerol-3-phosphate in the presence of ATP. The glycerol-3-phosphate is subsequently oxidized by Glycerol phosphate oxidase (GPO) to Dihydroacetone phosphate. This final step in the series of reaction is the reaction of hydrogen peroxide, 4-aminophenazone, and 4-chlorophenol, to form the indicator quinoneimine, as well as hydrochloric acid and water. It can be calculated by the equation given below. Triglycerides/5 = Total cholesterol-HDL-LDL

2.8 Assay of High-Density Lipoprotein (HDL) cholesterol concentration

High density lipoprotein (HDL) concentration in the serum sample was measured by selectively precipitating the Chylomicrons, VLDL and LDL with Phosphotungstate and Magnesium reagent (a precipitating agent) at room temperature, according to the method of Friedwald. In this method, 0.1 mL of the precipitating agent was added to 0.1 mL of serum. This was allowed to stand for 5 minutes after mixing 25°C and centrifuged at 1000 Xg for 15 minutes to obtain clear supernatant. The supernatant obtained contains HDL-cholesterol. The cholesterol content of HDL fraction which remained in the supernatant was determined by the endpoint method already described for serum cholesterol level estimation.

2.9 Assay of Very Low Density Lipoprotein (VLDL)-Cholesterol Concentration: The concentration of very low density lipoprotein (VLDL)-cholesterol in the sample was estimated by calculation described by Burstein and Sammaille, (1960). In this method, theVLDL-cholesterol level may be obtain dividing the serum triacylglycerol value by five. The factor, five is used on the basis that in fasting subjects with triacylglycerol concentration of 400 mg/dl, the VLDL value to triacylglycerol ratio is fixed at 1:5.VLDL cholesterol(mg/dl) = Triacylglycerol (mg/dl) ÷ 5. VLDL-cholesterol (mmol/l =Triacylglycerol (mmol/l) ÷ 2.2.This method has also been adopted by Browner (1 993), to determine the concentration of VLDL in plasma. However, the author maintained that the relationship holds best when triglyceride level is within the level of the 500 ± 1 00 mg/1 00 mL

2.10 Assay of serum low density lipoprotein (LDL)-cholesterol concentration: Serum low density lipoprotein (LDL)-cholesterol level was estimated by Friedwalds et al, (1972) methods. In the Friedwald's relationship, LDL-cholesterol is derived from the difference between the total serum cholesterol and the sum of HDL-cholesterol (HDL-C) and VLDL cholesterol (VLDL-C). LDL-cholesterol = Total cholesterol – (HDL-C + VLDL-C)

3.0 RESULTS AND DISCUSSION

Investigating the active compounds within the nut extract can help identify the specific components responsible for lipid profile improvements. Tetracarpidum Conophorum Nut Extract is found to positively influence the lipid profile of rats, because the extract possess anti-inflammatory and antioxidant properties, which can counteract the inflammatory and oxidative stress associated with obesity, this contributes to better lipid profiles and overall health. High-fat diets and obesity often lead to hepatic lipid accumulation and non-alcoholic fatty liver disease (NAFLD). Assessing the impact of the extract on the lipid profile can provide insights into its potential for promoting liver health and preventing liver disorders Understanding how Tetracarpidum Conophorum Nut Extract affects the lipid profile of Wistar albino rats can shed light on its potential as a natural remedy for managing obesity-related lipid abnormalities. Tetracarpidum Conophorum Nut Extract offers a positive impact on the liver, reducing hepatic lipid accumulation and improving liver function in the obese rats.

The result of the lipid profile of the experimental animals shows that some fractions of *Tetracarpidium Conophorum* can down regulate serum lipids as shown in Figure 3 below. The result shows that there was no significant difference in the lipid profile of the obese animals (Obsc) relative to the normal (NC). Equally the Obsc group treated with standard anti-obesity drug (orlistat) did not show any significant ($p < 0.05$) change relative to ObC. However, Total cholesterol, HDL-c, and LDL-c decreases and VLDL-c, HDL-TC and LDL-HDL ratios of Obsc increases relative to ObC group, also the changes were insignificant ($p < 0.05$), upon treatment with the different fractions of the *Tetracarpidium conophorum* nuts, though EWE treated group shows decrease in all the lipid fractions relative to controls and EAE group shows increase in total cholesterol, triacylglycerols, LDL-c and VLDL-c, while HDL-c decrease relative to Obsc. Further increases were observed in total cholesterol, HDL-C, LDL-C of ER treated group, besides TGs and VLDL that decreases relative to control. In

all the changes, there was no significant ($p < 0.05$) change between the controls and the treated groups.

Table 2. BMI classification of adult weights based on WHO Schema (BMI = weight in kg/height in meters^2)[3].

Classification	BMI (kg/m^2)	Risk of co-morbidities
B2.5 Underweight	<18.5	Low (but risk of other clinical problems increased)
Normal weight	18.5-24.9	Average
Overweight	25.0-29.9	Mildly increased
Obese	≥30	
Obese I	30.0-34.9	Moderate
Obese II	35.0-39.9	Severe
Obese III	≥40	Very severe

The result from this experiment shows that there was a decrease in TC, HDL-C and LDL-C of Obsc group relative to Obc group, though the decrease was insignificant, the result is in agreement with Bestille et al. (2009). The lipid profile was favourably decreased further upon treatment with Tetracarpidium conophorum nut extract of EWE (Kanu et al.2015) supported this finding. Meanwhile, when the obese animals were treated with the EAE fraction, total cholesterol, TGs, LDL-C and VLDL increases, while HDL-C and HDL, LDL decreases. Similarly, ER extract treated group increases in total cholesterol, HDL-C, LDL-C and LDL: HDL ratio, while decrease was observed in TGs and HDL:TC ratio all changes compared to the controls were insignificant ($p < 0.05$).

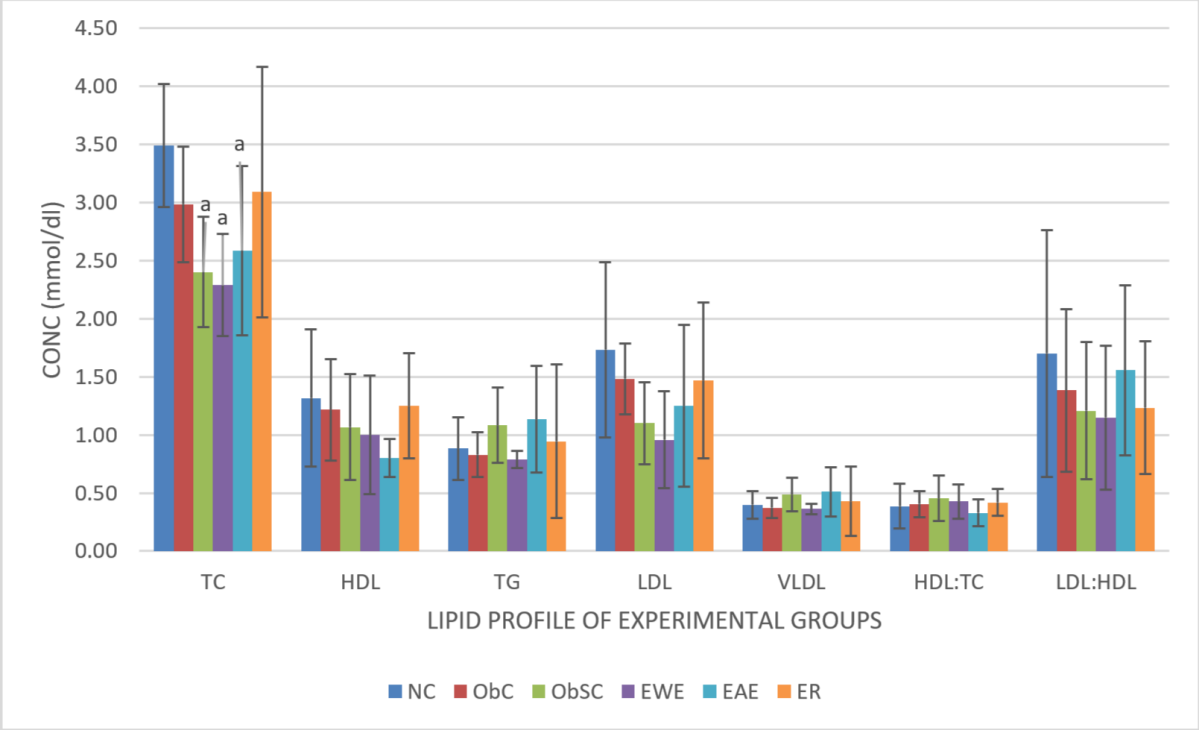


Figure 3: Showing the lipid profile and derived indices of experimental animal.

Values expressed in Mean ± SD, n = 7.

a= significant ($p < 0.05$) vs NC.

NC = Normal Control

Obc = obese control

Obsc = Obese standard control

EWE = Ethanol whole extract

EAE = Ethyl acetate extract

ER = Ethanol extract residue

The disparity of the effect of the treatment on the lipid profile of the treatment groups indicates the difference in the composition of bioactive molecules in the various extracts and perhaps EWE fraction has the phytochemical principle suspected to be responsible for the lipid profile ameliorating effect of walnut.

The most notable phytochemical besides the essential fatty, linoleic acid and α-linolenic acids in walnut (Deidre et al. 2009, Kanu et al. 2015, and Alasalvar et al., 2015) suspected to have this total cholesterol and LDL-C lowering effect are phenolic compounds like tannins e.g.

Ellagetannins (Sanchez-Gonzalex et al. 2015). Which have beneficial effects on cholesterol Concentrations and other CVD risk factors (Deidre et al 2009).
The inability of the ER extract to decrease LDL-C shows that it has lost the bioactive substances to the EWE and EAE fractions during extraction process. Triacylglycerol (TGs) and VLDL-Cconcentrations were raised in ObSC group relative to the ObC group. This also applies to the group treated EAE fraction. The concentrations decreases insignificantly upon treatment with EWE and ER fractions with EWE showing a better tendency to lower TGs and VLDL-C which are highly atherogenic. This implies that the capacity for Tetracarpidium Conophorum to lower VLDL-C and triglycerides is domiciled in the EWE and ER fractions.

4.0 CONCLUSION

This study investigated the effect of the different fractions of Tetracarpidium Conophorum on the lipid profile of MSG induced obese rats. Obesity as earlier defined, is the accumulation of fats thatmay impair health (WHO, 2015). Obesity comes with co-morbidities such as cardiovascular disease (CVD), diabetes (excess blood sugar), muscular disorder, some cancers including breast, overian, liver, gallbladder, kidney, and colon (Olawoore et al., 2016). Obesity have also been identified not just as a disease but also as a risk factor for other diseases, hence making obesity a health challenge. From the results, it can be concluded that the administration of *Tetracarpidium Conophorum* in experimental animal (albino wistar rats) in regard to lipid profile shows that there was no significant effect on the lipid profile of the Obese animals (Obc) administered African walnut extract over the 6-weeks period.

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