

Changes in the Weight, Plasma Lipid Profile, and Atherogenic Indices of Salt-Loaded Rats by Aqueous Extract of *Acalypha wilkesiana* Muell Arg: Potential for Cardiovascular Risk Reduction.

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ABSTRACT

The effect of aqueous extract of *Acalypha wilkesiana* leaves on the body and organ weights, plasma lipid profiles, and atherogenic indices of salt loaded rats was investigated. The control group received a diet consisting 100% of the commercial feed, while the four test groups received a diet consisting 8% salt and 92% commercial feed, except for the reference treatment group that had its salt-loading discontinued after six weeks. The extract was orally administered daily at 200 and 250mg/kg body weight; while the test control, reference, and control groups received appropriate volumes of water by the same route. The 200mg/kg treatment lowered (but not significantly) weight gain, significantly ($p < 0.05$) elevated plasma triglyceride levels above values before treatment, and produced significantly ($p < 0.05$) higher plasma HDL cholesterol and significantly ($p < 0.05$) lower plasma LDL and non-HDL cholesterol levels, cardiac risk ratio and atherogenic coefficient, compared to the other groups. These results suggest a possible dose dependent protective role of the extract against the development of cardiovascular diseases, and the management of dyslipidemic conditions, whether primary or secondary to hypertension.

(Keywords: *Acalypha wilkesiana*, atherogenic indices, dyslipidemia, lipid profile, salt-loading, weight control)

INTRODUCTION

One of the world's most common causes of mortality is coronary heart disease or cardiovascular disease. Its risk factors include: hyperlipidemia (or dyslipidemia), hypertension, and obesity [Martirosyan *et al.*, 2007]. Hyperlipidemia may be secondary to associated

conditions like medications, hypertension or obesity, or may be primary, as in genetic hyperlipidemias [Kavey *et al.*, 2006].

A consistent body of evidence from large clinical trials has established beyond doubt that lipid lowering can reduce the incidence of coronary events and stroke in a broad spectrum of individuals [Libby, 2001; Brunzell *et al.*, 2008]. Therefore, any nutritional and pharmacologic intervention that improves or normalizes abnormal lipid metabolism may be useful for reducing the risk of cardiovascular diseases [Zicha *et al.*, 1999; Shen, 2007]. Several drugs are at present, available for the management of dyslipidemia. However, there is presently, a renewed interest in the use of herbal products.

Acalypha wilkesiana Muell Arg, a member of the Euphorbiaceae family is one of the plants used in traditional medicine practice for the management of hypertension. The practitioners in Southern Nigeria administer the leaves for the control of hypertension. However, the mechanism of action of the leaves is yet to be clearly understood. In pursuance of this, we earlier undertook the study of the effect of the leaves on: plasma sodium and potassium levels of normal rabbits [Ikwuchi *et al.*, 2008]; blood pressure and aorta contractility [Ikwuchi *et al.*, 2009a], urinary and plasma chemistry [Ikwuchi *et al.*, 2009b], tissue profiles of ATPases [Ikwuchi and Ikwuchi, 2009a] and lactate dehydrogenase, pyruvate kinase, and acid and alkaline phosphatase [Ikwuchi *et al.*, 2010], of salt-loaded rats.

In this study, the effect of aqueous extract of the leaves of *A. wilkesiana* on the body and organ weights, plasma lipid profile and atherogenic indices of salt-loaded rats was investigated.

MATERIAL AND METHODS

Collection of Animals and Preparation of Plant Extract

Albino rats were collected from the animal house of the Department of Physiology, University of Nigeria, Enugu Campus, Enugu, Nigeria. Samples of the fresh *Acalypha wilkesiana* Muell Arg leaves were collected from within the Choba and Abuja Campuses of University of Port Harcourt, Port Harcourt, Nigeria. After due identification at the University of Port Harcourt Herbarium, Port Harcourt, Nigeria, they were cleaned of dirt, oven dried at 55°C, and ground into a powder. The resultant powder was soaked in boiled distilled water for 12h, after which the resultant mixture was filtered and the filtrate, hereinafter referred to as the aqueous extract, was stored for subsequent use. A known volume of this extract was evaporated to dryness, and the weight of the residue used to determine the concentration of the filtrate, which was in turn used to determine the dose of administration of the extract to the test animals.

Experimental Design

The rats were randomly sorted into five groups of five animals each, so that the average weights per group were approximately equal. The animals were housed in plastic cages. After a one-week acclimatization period on guinea growers mash (Port Harcourt Flour Mills, Port Harcourt, Nigeria), the treatment commenced and lasted for seven weeks. The control group received a diet consisting 100% of the commercial feed, while the four test groups received a diet consisting 8% salt and 92% commercial feed. The 8% dietary salt-loading was adapted from Obiefuna *et al.* [1991]. At the end of the sixth week, the rats were weighed, then fasted overnight and their plasma triglyceride levels were determined (using test strips, with blood from tail cuts), before commencing the administration of the extract.

The first test group (AWT20) received daily by intra-gastric gavages 200mg/kg body weight of the *Acalypha wilkesiana* extract; the second group (AWT25) received 250mg/kg body weight of the extract; while the other three groups, test control, reference treatment (reference) and control groups received appropriate volumes of water by the same route. The animals were

allowed food and water *ad libitum*. At the end of the one week treatment period, the rats were weighed, fasted overnight, and anaesthetized by exposure to chloroform. While under anesthesia, they were painlessly sacrificed and blood was collected from each rat into heparin sample bottles. Whole blood was used to determine the triglyceride levels (using test strips), the heparin anti-coagulated blood samples were centrifuged at 1000g for 10min, after which their plasma was collected and stored for subsequent analysis.

Determination of the Plasma Lipid Profiles/Indices

Plasma triglyceride concentration (TG) was determined using multiCarein™ triglyceride strips and glucometer (Biochemical Systems International, Arezzo, Italy). The test is based on lipase/glycerol kinase/glycerol phosphate oxidase/peroxidase/chromogen reaction. The intensity of the colour developed from the reaction is proportional to the concentration of triglycerides in the blood. Plasma total and high density lipoprotein cholesterol concentration (TC and HDLC) were assayed enzymatically with Randox commercial test kits (Randox Laboratories, Crumlin, England).

In the presence of magnesium ions, low density lipoproteins (LDL and VLDL) and chylomicrons fractions were precipitated quantitatively by the addition of phosphotungstic acid. After centrifugation, the cholesterol concentration of the high density lipoprotein (HDL) fraction, which remained in the supernatant, was determined, as in total cholesterol. The cholesterol released by enzymatic hydrolysis was oxidized with the concomitant release of hydrogen peroxide, whose breakdown led to the conversion of 4-aminoantipyridine to quinoneimine (the indicator) whose concentration was determined spectrophotometrically at 500nm.

Plasma VLDL- and LDL-cholesterol (LDLC and VLDLC) concentrations were calculated using the Friedewald equation [Friedewald *et al.*, 1972] as follows:

- $LDLC \text{ (mmol/L)} = TC - HDLC - \frac{TG}{2.2}$
- $VLDLC \text{ (mmol/L)} = \frac{TG}{2.2}$

While the plasma non-HDL cholesterol concentration was determined as reported by Brunzell *et al.* [2008]:

- Non-HDLC = TC – HDLC

The atherogenic indices were calculated as earlier reported by Ikewuchi and Ikewuchi [2009b] using the following formulae:

- Cardiac Risk Ratio = $\frac{TC}{HDLC}$
- Atherogenic Coefficient = $\frac{TC - HDLC}{HDLC}$
- Atherogenic Index of Plasma = $\log \frac{TG}{HDLC}$

Determination of Organ Weights and Sizes

The carcasses of the rats were dissected and their lungs, kidney, heart, and liver were collected and weighed. The sizes of the organs were also determined, by water displacement method, using an eureka can.

Statistical Analysis of Data

All values are quoted as the mean ± SEM. The values of the various parameters for the test and control groups were analyzed for statistical significant differences using the student's t-test, with the help of SPSS Statistics 17.0 package. P<0.05 was assumed to be significant.

RESULTS AND DISCUSSION

The effect of aqueous extract of *A. wilkesiana* on mean daily weight gain and organ sizes and weights, is shown in Tables 1 and 2. There were no significant differences in the weight gains of the animals before administration. The administration of the extract produced lower (though not significantly) mean daily weight gains, compared to the control, test control and reference, as well as the corresponding values before treatment. There were no significant differences in the sizes of the heart, kidney, liver and lungs, as well as the liver weights of all the animals.

Table 1: Effect of Aqueous Extract of *Acalypha wilkesiana* on the Body and Organ Weights of Salt Loaded Rats.

<i>Parameter</i>	<i>Control</i>	<i>Test control</i>	<i>Magnitude Reference</i>	<i>AWT20</i>	<i>AWT25</i>
Daily Weight Gain					
➤ BA (g/day)	0.948±0.243 ^a	0.997±0.064 ^a	1.309±0.228 ^a	1.039±0.377 ^a	0.721±0.156 ^a
➤ AA (g/day)	0.975±0.820 ^a	1.081±0.355 ^a	1.900±1.155 ^a	-2.734±1.248 ^a	-0.313±0.803 ^a
➤ % change	-0.176±63.599 ^a	0.765±31.991 ^a	-2.854±130.464 ^a	-432.692±59.058 ^b	-162.956±109.647 ^a
Heart					
➤ Weight (g)	0.494±0.037 ^{a,b}	0.392±0.009 ^a	0.527±0.035 ^b	0.487±0.043 ^{a,b}	0.453±0.038 ^{a,b}
➤ Size (cm ³)	0.700±0.200 ^a	0.375±0.025 ^a	0.475±0.125 ^a	0.600±0.100 ^a	0.500±0.150 ^a
Kidney					
➤ Weight (g)	0.842±0.064 ^a	0.688±0.028 ^b	0.877±0.067 ^{a,b}	1.000±0.053 ^a	0.950±0.093 ^{a,b}
➤ Size (cm ³)	1.000±0.100 ^a	0.650±0.150 ^a	0.950±0.050 ^a	1.000±0.050 ^a	0.950±0.150 ^a
Liver					
➤ Weight (g)	5.311±0.310 ^a	4.830±0.155 ^a	5.609±0.460 ^a	5.224±0.499 ^a	5.352±0.447 ^a
➤ Size (cm ³)	3.800±0.300 ^a	3.350±0.350 ^a	5.800±0.100 ^a	5.050±0.850 ^a	4.375±1.075 ^a
Lung					
➤ Weight (g)	1.378±0.165 ^a	0.958±0.078 ^b	1.324±0.233 ^{a,b}	1.790±0.353 ^{a,b}	1.521±0.210 ^{a,b}
➤ Size (cm ³)	1.975±0.825 ^a	0.875±0.075 ^a	2.35±1.250 ^a	2.000±0.700 ^a	1.900±0.700 ^a

Values are mean ± SEM, n=5, per group. Values in the same row with the different superscripts are significantly different at p<0.05; ‡ p<0.05 compared to baseline (before administration). AA = after administration, BA = before administration. % change = percentage change from baseline value (i.e. before administration).

Table 2: Effect of Aqueous Extract of *Acalypha wilkesiana* on Organ/Body Weight Ratio of Salt Loaded Rats.

Parameter	Magnitude				
	Control	Test control	Reference	AWT20	AWT25
HBR	0.0029±0.0001 ^a	0.0029±0.0001 ^a	0.0032±0.0005 ^a	0.0031±0.0001 ^a	0.0030±0.0004 ^a
KBR	0.0049±0.0002 ^a	0.0052±0.0001 ^a	0.0053±0.0010 ^{a,b}	0.0060±0.0002 ^b	0.0062±0.0007 ^{a,b}
LBR	0.0310±0.0008 ^a	0.0369±0.0009 ^b	0.0332±0.0050 ^{a,b}	0.0333±0.0013 ^a	0.0356±0.0050 ^{a,b}
LGBR	0.0081±0.0011 ^{a,b}	0.0073±0.0005 ^a	0.0084±0.0024 ^{a,b}	0.0111±0.0013 ^{a,b}	0.0095±0.0008 ^b

Values are mean ± SEM, n=5, per group. Values in the same row with the different superscripts are significantly different at p<0.05. HBR = Heart/body weight ratio; KBR = Kidney/body weight ratio; LBR = Liver/body weight ratio; LGBR = Lung/body weight ratio.

The kidney weight of AWT20 was significantly (p<0.05) higher than test control, but not significantly different from control, reference and AWT25. The heart and lung weight of the test groups did not differ significantly from the control, test control and reference. There were no significant differences in the heart/body weight ratios of all the animals. The kidney and liver/body weight ratios of AWT20 were respectively, significantly (p<0.05) higher and lower than the test control values, but not different from the control, reference and AWT25. The lung/body weight ratio of AWT25 was significantly higher than the test control, but not different from the control, reference treatment and AWT20. The present results corroborates our earlier [Ikewuchi *et al.*, 2009b] report of the weight reducing effect of *Acalypha wilkesiana* leaf meal on salt-loaded rats.

Weight reduction is one of the means of alleviating coronary risk incidence, dyslipidemia, hypertension and obesity [Mertens and Van Gaal, 2000; Trussell *et al.*, 2005; Krauss *et al.*, 2006], and is one of the strategies for increasing low HDL-cholesterol levels [NCEP, 2002; Assmann and Gotto, 2004]. In this study, the lower mean daily weight gain observed in the test animals may be due to the diuretic effect of the leaves [Ikewuchi *et al.*, 2009b], and supports the use of the leaves in the management of hypertension, as well as suggesting its use in the management of obesity and dyslipidemia; and by extension, the reduction of cardiovascular risk.

The effect of aqueous extract of *A. wilkesiana* on the plasma triglyceride levels of salt-loaded rats is given in Table 3. There were no significant differences in the plasma triglyceride levels of all the groups, before and after treatment. The plasma triglyceride levels of the control and

AWT20 were significantly (p<0.05) lower and higher respectively, than their values before treatment. The change in plasma triglyceride level of AWT25 was significantly (p<0.05) higher than the control, but not different from the test control, reference and AWT20.

Table 4 shows the effect of aqueous extract of *A. wilkesiana* on the plasma lipoprotein cholesterol profiles of salt-loaded rats. There were no significant differences in the plasma total and VLDL cholesterol levels of the rats. The plasma HDL cholesterol levels of AWT20 was significantly higher than other groups; while the plasma LDL and non-HDL cholesterol levels of AWT20 were significantly lower than other groups. High plasma levels of LDL cholesterol is a risk factor for cardiovascular disease [Ademuyiwa *et al.*, 2005; Lichtenstein *et al.*, 2006] and often accompanies hypertension [Zicha *et al.*, 1999; Shepherd, 1998]: while decreases in plasma LDL cholesterol have been considered to reduce risk of coronary heart disease [Rang *et al.*, 2005; Shen, 2007]. In this study, we observed a significantly lower plasma LDL cholesterol levels in the animals given 200mg/kg body weight, indicating the likely cardio-protective effect of the extract at that dose.

Decreased plasma HDL cholesterol is a risk factor for cardiovascular diseases [Rang *et al.*, 2005; Martirosyan *et al.*, 2007; Lichtenstein *et al.*, 2006; Lewis and Rader, 2005] and is often found in hypertension [Zicha *et al.*, 1999; Shepherd, 1998]. However, Increases in plasma HDL cholesterol have been considered to reduce risk in coronary heart disease [Rang *et al.*, 2005; Assmann and Gotto, 2004].

Table 3: Time Course of the Effect of Aqueous Extract of *Acalypha wilkesiana* on the Plasma Triglyceride Levels of Salt-Loaded Rats.

Time/Parameter	Magnitude				
	Control	Test control	Reference	AWT20	AWT25
Before treatment (mmol/L)	1.590±0.171 ^a	1.277±0.069 ^a	1.204±0.034 ^a	1.453±0.135 ^a	1.165±0.052 ^a
After treatment (mmol/L)	1.272±0.152 ^{a,‡}	1.641±0.280 ^a	1.610±0.304 ^a	1.910±0.191 ^{a,‡}	1.305±0.113 ^a
Change					
➤ (mmol/L)	-0.318±0.111 ^a	0.364±0.221 ^{a,b}	0.406±0.324 ^{a,b}	0.456±0.131 ^b	0.140±0.107 ^b
➤ (%)	-19.267±7.309 ^a	25.012±16.328 ^{a,b}	36.311±28.933 ^{a,b}	32.451±10.111 ^b	12.385±8.602 ^b

Values are mean ± SEM, n=5, per group. Values in the same row with the different superscripts are significantly different at p<0.05; ‡ p<0.05 compared to value before treatment.

Table 4: Effect of Aqueous Extract of *Acalypha wilkesiana* on Plasma Lipoprotein Cholesterol Profile of Salt-Loaded Rats.

Lipid	Plasma concentration (mmol/L)				
	Control	Test control	Reference	AWT20	AWT25
Plasma total cholesterol	3.977±0.165 ^a	5.440±0.651 ^a	4.509±0.201 ^a	4.132±0.135 ^a	3.906±0.389 ^a
Plasma HDL cholesterol	1.709±0.494 ^{a,b}	1.235±0.093 ^a	1.430±0.314 ^{a,b}	2.431±0.346 ^b	1.407±0.066 ^a
Plasma VLDL cholesterol	0.578±0.069 ^a	0.746±0.127 ^a	0.732±0.138 ^a	0.868±0.087 ^a	0.593±0.051 ^a
Plasma LDL cholesterol	1.691±0.457 ^{a,b}	3.459±0.689 ^a	2.347±0.209 ^a	0.833±0.216 ^b	3.369±0.712 ^a
Plasma non-HDL cholesterol	2.268±0.463 ^{a,b}	4.205±0.654 ^a	3.079±0.253 ^a	1.701±0.234 ^b	3.962±0.737 ^a

Values are mean ± SEM, n=5, per group. Values in the same row with the different superscripts are significantly different at p<0.05.

High HDL exerts a protective effect by decreasing the rate of entry of cholesterol into the cell via LDL and increasing the rate of cholesterol release from the cell [Marcel *et al.*, 1980], i.e., by promoting reverse cholesterol transport through scavenging excess cholesterol from peripheral tissues, and subsequent esterification using lecithin: cholesterol acyltransferase, and deliverance to the liver and steroidogenic organs for synthesis of bile acids and lipoproteins, and eventual elimination from the body [Assmann and Gotto, 2004; Ademuyiwa *et al.*, 2005]; and inhibiting the oxidation of LDL as well as the atherogenic effects of oxidized LDL by virtue of its antioxidant [Brunzell *et al.*, 2008; Assmann and Gotto, 2004; Ademuyiwa *et al.*, 2005] and anti-inflammatory property [Ademuyiwa *et al.*, 2005]. So, the high plasma HDL cholesterol level, recorded for the AWT20 group, in the present study, is indicative of the cardioprotective effect of the extract, at least, at a dose of 20mg/100g body weight. Several studies have shown that non-HDL cholesterol is a better predictor of cardiovascular disease risk than is LDL cholesterol [Liu *et al.*, 2005; Pischon *et al.*, 2005; Brunzell *et al.*, 2008].

Therefore, the significantly lower plasma non HDL cholesterol observed in the AWT20 group indicates the ability of the extract (at 200mg/kg body weight), to reduce cardiovascular risk.

The effect of aqueous extract of *A. wilkesiana* on atherogenic indices of salt-loaded rats is shown in Table 5. The cardiac risk ratio and atherogenic coefficient of AWT20 was significantly (p<0.05) lower than the other groups. There were no significant differences in the atherogenic index of plasma of the animals. Atherogenic indices are strong indicators of the risk of heart disease: the higher the value, the higher the risk of developing cardiovascular disease and vice versa [Brehm *et al.*, 2004; Dobiášová, 2004; Usoro *et al.*, 2006; Martirosyan *et al.*, 2007]. According to Usoro *et al.* [2006], low atherogenic indices are protective against coronary heart disease.

CONCLUSIONS

In this study, we observed that the extract, administered at 200mg/kg body weight, produced significantly lower cardiac risk ratio and atherogenic coefficient.

Table 5: Effect of Aqueous Extract of *Acalypha wilkesiana* on Atherogenic Indices of Salt-Loaded Rats.

Index	Magnitude				
	Control	Test control	Reference	AWT20	AWT25
Cardiac risk ratio	3.551±1.375 ^a	3.459±0.689 ^a	4.057±0.832 ^a	1.843±0.202 ^b	2.770±0.224 ^a
Atherogenic coefficient	2.551±1.375 ^a	2.459±0.689 ^a	3.057±0.832 ^a	0.843±0.202 ^b	1.770±0.224 ^a
Atherogenic index of plasma	-0.057±0.158 ^a	0.096±0.107 ^a	0.078±0.143 ^a	-0.093±0.093 ^a	-0.038±0.034 ^a

Values are mean ± SEM, n=5, per group. Values in the same row with the different superscripts are significantly different at p<0.05.

This effect is comparable to that reported for *Tridax procumbens* on cholesterol loaded rats [Ikewuchi and Ikewuchi, 2009c].

In conclusion, all of these results indicate a likely potential dose dependent protective mechanism of the extract against the development of atherosclerosis and coronary heart disease, as well as dyslipidemic conditions, whether primary or secondary to hypertension. It also implies that the extract may help manage the dyslipidemic conditions, which according to Salvetti and Ghiadoni [2006], accompany the administration of thiazide diuretics.

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