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ASSESSMENT OF LIPID, HAEMATOLOICAL AND COAGULATION PARAMETERS FOLLOWING ORAL ADMINISTRATION OF *Ficus Capensis* IN MALE ALBINO RATS

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Abstract
Abnormal blood coagulation and hyperlipidemia remain the main cause of cardiovascular diseases. Despite the numerous and long-term use of *Ficus Capensis* as a medicinal plant in South East Nigeria, there is limited information on its effect on coagulation parameters. This study is aimed at evaluating the effects of oral administration of methanol extract of *F. Capensis* on lipid, hematological and coagulation parameters in male albino rats. A total of twenty four (24) male Wister albino rats weighing 180 – 200g were divided into 4 groups of 6 rats each. The test groups (2, 3 and 4) received orally graded doses (100, 200 and 400mg/kg body weight) of methanol extract of *Ficus Capensis* for 4 weeks, while group 1 (control) was given 0.5ml normal saline for the same period. At the end of the experimental period, animals were sacrificed; blood sample was collected by cardiac puncture for the estimation of selected biochemical parameters. The results showed a significant increase ($P<0.05$) in body weight, haematological parameters tested, high density lipoprotein, and prolongation of clotting time (CT), prothrombin time (PT) and activated partial thromboplastin time (a PTT) when compared with the control group. A significant ($P<0.05$) decrease in the concentration of total cholesterol, triglyceride, low density lipoprotein and very low-density lipoprotein was also observed. This study has demonstrated a dose related prolongation of PT, APTT, CT, decrease in lipid and increase in haematological parameters by methanol extract *Ficus Capensis* which may be beneficial in the management of Cardiovascular related diseases.

Keywords: Coagulation, *Ficus Capensis*, haematology, Cardiovascular, Hyperlipidemia

Introduction

Hyperlipidemia refers to several disorders that can result when there are elevated levels of serum lipids in the blood. Excess lipids which are transported in blood within lipoprotein particles can enter the walls of the arteries and increase the risk for developing hardening of the arteries, which could cause complications such as coronary heart disease. Rupture of atherosclerotic plaques induces the formation of intravascular thrombi that may occlude blood flow and lead to myocardial infarction and stroke (Philip *et al*., 2014). Hence hyperlipidemia produces a pro-thrombotic state in animal models (Ballard-Lipka *et al*., 2012). Large epidemiological studies have demonstrated that subject with hypertension have a marked increase in the prevalence of hypertriglycerdemia and hypercholesterolemia (Kumar *et al*., 2008) which can also lead to abnormal blood clothing. Abnormal blood clotting is harmful because even minor vessel damage can lead to excessive blood loss. Overactive clotting is also detrimental because it will lead to thrombogenesis (formation of blood clots).

Plant materials have been used extensively to treat diseases associated with abnormal blood clotting, hyperlipidemia and various cardiovascular disorders in developing countries. Several plant extracts that possess therapeutic potential for the treatment of cardiovascular diseases such hypertension, arteriosclerosis, ischemic heart disease and congestive heart failure have been identified. Many researchers have also validated the medicinal claim of some natural products of plants origin and its beneficial effect in the development of new therapeutic agents (Alamgir *et al.,* 2017; Upendra *et al.,* 2010). A good number of medicinal plants are traditionally employed to manage and treat lipid, blood circulation and coagulation disorder. Over the past few decades, numerous anticoagulant drugs have been applied for clinical treatment; however, the low toxicity advantage of natural agents has become a great interest in anticoagulant research.

Ficus capensis which belongs to the *Moraceae* family is commonly found in Nigeria and some West African countries. It is called *Uwaryara* in Hausa, *Opoto* (Yoruba), and *Akokoro* (Igbo), fast-growing, deciduous ever green tree. Almost all the parts have been found useful for treating various diseases and promote vascular health (Njoku *et al*., 2017). Ethno-medicinal uses of *F. capenesis* have shown their anti-cancer, anti-imflamatory and anti-diabetic activities (Nawaz *et al.,* 2019). Scientifically, the leaves, stems and seeds have been reported to perform multiple biological activities in animals such as antisickling of red blood cells (Mpiana *et al.,* 2008 ; Umeokoli *et al.,* 2013), antibacterial (Oyeleke *et al.,* 2013; Musa *et al*., 2017), anti-diarrhoeal (Owolabi *et al*., 2019), anti-lipidemia (Musa *et al*., 2019) and anti-anemia and blood boosting (Ezeigwe *et al.,* 2020). This study was conducted to investigate the effect of methanol extract of *F. capenesis* on blood coagulation, lipid and hematological parameters in male albino rats.

Materials and Methods

Sample preparation and extraction

Fresh and matured leaves of *F. Capensis* were harvested within the farm in Amaekpu Ohafia in Ohafia Local Government Area, Abia State, Nigeria. The leaves were thoroughly washed under running tap water to remove unwanted particles, after which they were cut into pieces, dried for 4weeks at room temperature and finally the dried leaves were ground into powder using manual grinding machine (Corona). Five hundred grammes (500g) of the ground sample powder of *F.* capensis was soaked in 1Lof 80% Methanol for 72h at room temperature accompanied by intermittent shaking for complete extraction of the bioactive constituents. The soaked sample in methanol was sieved using clean white handkerchief and filtered using Whatman No.1 (125mm) filter paper. The filtrates were concentrated using water bath at 50°C. Concentrated methanol extact of *F. Capensis* were stored in labeled airtight container in a refrigerator at 4°C until use. The yield of the crude extract was 16.32%.

Experimental Animals

Wistar albino rats (male) weighing 180-200g were obtained from the animal breeding house, College of Veterinary medicine, Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria and kept as experimental animal for 14 days acclimatization period. They were also maintained under 12hrs light/dark cycles at room temperature with standard rat diet and offered water *adlibitum*. Animal care and handling, as well as experimental protocols were duly followed in accordance with the National Institute of Health Guidelines for the care and use of laboratory animals (National Research Council (US) Committee update) and Institute for Laboratory Animal Research (ILAR).

Experimental Design

Acclimatized normal animals (180-200g) were divided into 4 groups of 6 rats each. The test groups (2, 3 and 4) were given orally by gavage for 4 weeks with graded doses (100, 200 and 400mg/kg bwt of methanol extract of *F.capensis,* per day respectively, while group 1 served as the control and was given 0.5ml normal saline for the same period. The experimental administration of the plant extract was conducted between the hours of 7-9am daily. Good hygiene was maintained by constant cleaning of the cages and the experimental environment. All the animals were weighed before the commencement of the treatment and on weekly basis. At the end of the experimental period, the animals were re-weighed and sacrificed by cervical dislocation, blood samples were collected by cardiac puncture into EDTA bottles and some in centrifuge tubes containing 3.2% Sodium citrate solution (1part of tri-sodium citrate solution: 9 parts of blood) and centrifuged at 3000g for 15min using Humax centrifuge to obtain pure platelet plasma (PPP) for blood coagulation assays (Foster *et al.,* 2009).

Determination of Prothrombin Time (PT)

Prothrombin Time was determined following the PT reagent (Diagen calcium brain thromboplastin) manufacturer's instruction according to the method of MacMillan and Brown (1954) with a slight modification. Calcium Rabbit Brain thromboplastin reagent (0.2ml) was was measured in a clotting tube placed in a water bath at 37°C and incubated for 1 to 2 min to reach 37°C. Plasma (0.1ml) was then added and a stop watch started. The tube was slightly tilted at regular intervals (returning to the water bath between tilting) until the formation of a clot was observed, watch was stopped and the time recorded.

Determination of Activated Partial ThromboplastinTime (aPTT)

This was done following the aPTT reagent (Diagen kaolin platelet substitute mixture) manufacturer's instruction. The reagent was reconstituted with 5ml distilled water, and 0.2ml of Kaolin platelet substituent mixture was measured into a clotting tube in a water bath at 37°C and incubated for1-2 min. After that, 0.1ml of test plasma was added and the tube gently tilted at intervals for exactly 2min. A 0.1ml of 0.025M calcium chloride (pre-incubated at 37°C) was added, while simultaneously starting a stop watch. Tilting of the tube at regular intervals continued until clot formation was observed, watch was instantly stopped and the time was recorded (Hapgood *et al.,* 2013).

Determination of Clotting Time

This was carried out using Ivy's method as reported by Ayodele *et al.* (2020). Blood was taken directly from the heart to avoid contamination with tissue thromboplastin (0.8ml from each rat). A 0.2ml of blood was then delivered into four glass test tubes that had previously been warmed and maintained at 37°C and the tubes immediately placed in a 37°C water bath to mimic the temperature of the internal environment. The stopwatch was started immediately the blood was delivered into the glass test tubes and the tubes were continually tilted at 40s intervals (until blood in them stopped flowing when tilted at an angle of 90°), starting with the first, to see and note the time when the blood clotted. The clotting time

was taken as the average of the times blood clotted in the four tubes.

Determination of Hematological Parameters

Blood samples were collected into EDTA bottles, gently mixed by reversing about 10 times and left to rest at room temperature for about 15min prior to analysis to enable the cells to stabilize ((Muriiti *et al.,* 2015). Hematological profile of the whole blood of experimental animals was done using a Swelab automatic Auto counter, AC970EO+ (Boule Medicals, Sweden).

Estimation of lipid parameters

Five milliliters of blood sample (5ml) were collected in plain tubes. Serum was immediately separated out by centrifugation at 3000rpm for 20min in 14K Humax centrifuge. Lipid profiles were analyzed on Humalyzer 3000 (Semi automated chemistry analyzer, model No. 16700, Human Germany) using standard kits supplied by Humax. Cholesterol and low density lipoprotein cholesterol (LDL-C) was estimated by CHOD-PAP method (Trinder, 1969). Triglyceride was estimated by GPO-PAP method and high density lipoprotein cholesterol (HDL-C) following the method of Warnick *et al.,* (1990).

Statistical Analysis

All the results were expressed as mean ± standard deviation (SD) in each of the four groups. (Six rats per group). Statistical analysis was performed using statistical package for social sciences (SPSS) version 21.0 software. The differences between treated and untreated groups were assessed by one way analysis of variance (ANOVA) followed by Duncan multiple comparison test (Duncan, 1955). Results were considered significant at P<0.05.

Results and Discussion

The body weight of rats measured at different weeks showed a significant increase (P< 0.05) in all the experimental groups (Fig. 1). The increase in body weight of normal rats that did not receive the extract was more prominent compared to the groups that were administered with graded doses of methanol extract of *F.capensis* leaves.

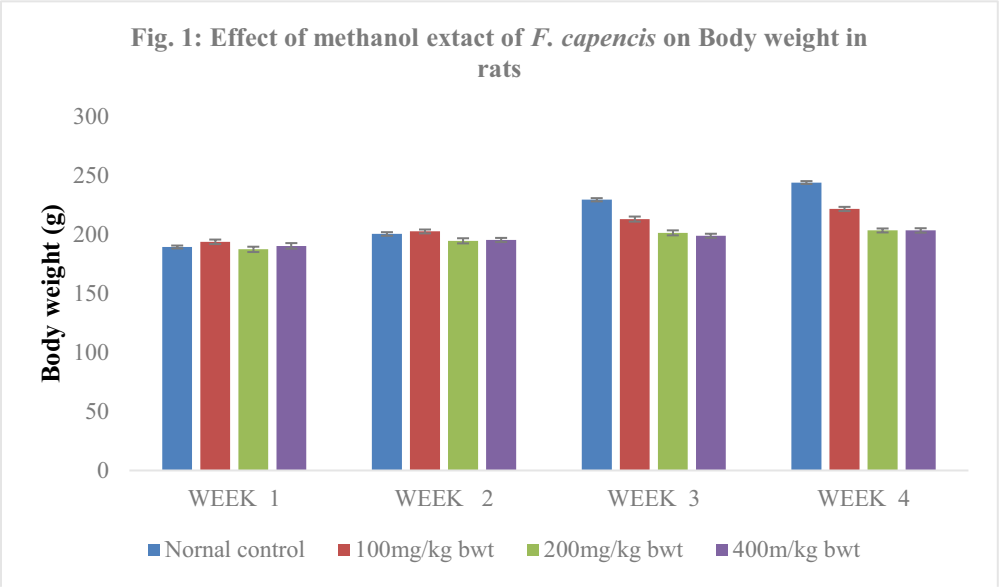

Figure 1: All values are expressed as mean ± SD for 6 rats per group

Table 1: Effect of methanol extract of *F. Capensis* on Lipid parameters in male Wistar albino rats

	Concentration off different Lipid Parameters (mg/dl)				
Groups	**TC**	**TG**	**HDL-c**	**LDL-c**	**VLDL-c**
Normal control 0.5ml of 0.90% normal saline	141.22±1.13^{a}	129.33±1.10^{a}	39.15±2.44^{a}	43.21±0.18^{a}	1.15±1.55^{a}
100mg/kg btw	101.11±1.22^{b}	118.51±1.53^{ab}	49.33 ±0.67^{a}	38.79±0.48^{ab}	0.16 ± 1.24^{c}
200mg/kg bwt	97.82±0.34^{c}	110.51±0.97^{a}	42.50±1.82^{a}	30.70±0.66^{b}	0.91±1.72^{ab}
400m/kg bwt	84.11±1.29^{c}	95.18±1.43^{b}	45.84±1.25^{ab}	22.45±1.67^{c}	0.46±2.17^{ab}

Values with different superscript are significantly different at P<0.05

The effect of oral administration of methanol extract of *F. capensis* leaves to normal rats at different doses is shown in Table 1. Result showed a significant (***P***<0.05) decrease in the concentration of total cholesterol, triglyceride, low density lipoprotein and very low-density lipoprotein and significant (***P***<*0.*05) increase in high-density lipoprotein when compared with the normal rats without extract administration. The effect of the extract on the lipid parameters was dose dependent as more reduction was observed in groups administered with higher concentration (400mg/kgbwt) of the extract.

Table 2: Effect of methanol extract of *F. capensis* on coagulation profiles of rats

Groups	CT(sec)	PT(sec)	aPTT(sec)
Normal control 0.5ml of 0.90% normal saline	75.85±1.18a	67.12±1.14a	95.33±1.60a
100mg/kg bwt	90.33 ± 1.2a	85.54±1.15b	102.16±1.33a
200mg/kg bwt	115.14±1.34b	93.34±0.27b	148.32±1.51c
400mg/kg bwt	135.11±2.17c	120.19±0.73c	194.55±1.32d

Values are mean ±SD, n=6. Values with different superscript are significantly different at P<0.05
CT= Clotting time, PT=Prothrombin time,aPTT= Activated partial thromboplastin time

The effect of methanol extract of *F.Capensis* (200 and400mg/kg body weight) on coagulation parameters of rats after 28 days showed that the extract increases the clotting time (CT), prothrombin time (PT) and activated partial thromboplastin time (a PTT) compared to control group (Table 2). The Prothrombin Time (PT) values in test groups (2,3 and 4) when compared with the control group (1)were found to be high and showed a significant difference ($p<0.05$).

Table 3: Effect of methanol extract of *F. capensis on* selected hematological parameters in rats

			Experimental Groups	
Hematological parameters	**Normal control 0.5ml of 0.90% normal saline**	**100mg/kg bwt**	**200mg/kg bwt**	**400mg/kg bwt**
RBC ($x10^{12}$ cells/L)	5.96 ± 1.15^{a}	6.18 ± 1.23^{b}	7.25 ± 1.42^{b}	7.88 ± 0.64^{b}
HB (g/dL)	12.16 ± 1.22^{a}	12.95 ± 1.12^{a}	13.88 ± 1.28^{b}	14.17 ± 0.99^{b}
PCV (%)	44.32 ± 0.98^{a}	50.48 ± 1.14^{b}	56.83 ± 0.78^{c}	58.65 ± 0.73^{c}
MCV (cell/L)	42.13 ± 0.54^{c}	48.23 ± 1.23^{c}	59.44 ± 1.17^{b}	62.12 ± 1.58^{a}
MCHC (g/cell)	28.44 ± 0.36^{a}	28.35 ± 1.52^{a}	28.56 ± 1.15^{a}	28.99 ± 1.74^{a}
Platelets	463.00 ± 1.77^{a}	462.00 ± 1.36^{a}	499.00 ± 0.86^{b}	567.00 ± 1.27^{c}
WBC($x10^{9}$ cell/L)	4.38 ± 1.64^{a}	5.19 ± 1.43^{b}	6.23 ± 0.72^{c}	6.98 ± 1.26^{c}

Values are mean ±SD, n=6. Values with different superscript are significantly different at P<0.05
RBC= Red blood cell, HB = Hemoglobin, PCV = Packed cell volume, WBC = White blood cell, MCHC = Mean corpuscular hemoglobin concentration, MCV = Mean corpuscular volume

The result in Table 3 showed a significant increase in hematological parameters under study. Administration of the extract at different dose levels of 100,200 and 400mg/kg body weight caused a significant increase in the levels of platelets, WBC, RBC, HB, PCV, MCV and MCHC.

There is a strong correlation between lipid profile and coagulation parameters, so abnormal alterations in lipid levels and coagulation parameters influences thrombosis. Anticoagulant treatment plays an important role in reducing the risk of thrombosis in normal and diseased states (Ayodele *et al.,* 2020). The result showed that the extract significantly reduced serum cholesterol, triglycerides, LDL-C, VLDL and elevated the level of HDL-C in male rats. Elevated levels of HDL concentration have a protective effect against atherosclerosis. High levels of serum cholesterol, triglycerides, LDL-C and VLDL increase the risk of cardiovascular diseases (Buch *et al.,* 2010). This reduction in the serum lipid profile levels may as well be attributed to reduced biosynthesis of cholesterol or inhibition of lipolysis. Similarly, the lipid lowering effect caused by the *F. capensis* extract is in agreement with results obtained by Michos *et al*. (2019).

The variation in weights gain of the rats might be due to the different concentration (100, 200 and 400m/kg bwt) of plant extract administered to the test animals. The decrease in weight gain following oral administration at higher concentration of the extract at the last week may be attributed to loss in muscle and adipose tissue resulting from breakdown of tissue protein and fatty acids (Pathak *et al*., 1991). Cardiovascular disease is a prominent killer. Some cardiovascular diseases like myocardial infarctions, stroke and thrombosis can arise from pathologies associated with coagulation (Lau *et al.,* 2009).Over activity of the coagulation cascade increases risk of thrombosis formation (Mekhfi *et al*., 2012). This can lead to thromboembolisms which block blood flow and lead to ischemia with subsequent damage to the afflicted organs (Norris *et al.,* 2003).

Blood clotting is an intricate cascade of reactions that involves many proteins (factors) which must act in an exact sequence to produce clot formation. The process is rapid and efficient and requires regulation because, if not controlled, excessive clotting can lead to thrombosis (Christokhodova *et al.,* 2020. Anticoagulants are chemical agents that interact with the body's natural blood coagulation system to treat and prevent abnormal blood clots like Deep vein thrombosis (DVT). They are also useful in controlling blood coagulation in both health and diseased conditions such as cardiovascular disease, diabetes mellitus and cancer (Chan *et al*.,1917) The higher values observed in CT, aPTT and PT in this study can be attributed to the reduction in the production of clotting factors or deficiency in the coagulation factor needed, hence extract of *F. Capensis* could be useful in combating the risk of vascular disease by decreasing the

fibrinogen level, reducing the activities of platelets and coagulation enzymes in circulation which are essential in generating thrombin. This is in line with the findings of Hossein *et al*. (2013) who also observed that reduction in CT, aPTT and PT may occur due the ability of plant extract to break down blood clot thus strengthening its anticoagulant potential.

Hematological parameters are used to access the effect of chemical compounds present in medicinal plants on blood system. Exposure of animals to toxicant from plant extract may induce a pathological condition to hematological indices of the blood system (Jorum *et al.,* 2016). In this study, the extract of *F. Capensis* increased the selected hematological parameters in rats. The observed increase may suggest that the extract could have stimulated erythropoietin release leading to the production of red blood cell and hemoglobin (Njoku-oji *et al.,* 2016). This justifies the use of *F.capensis* in folklore medicine as a blood tonic because of its blood boosting effect. White blood cells have been known to increase when there is infections or exposure of animal to toxic of foreign bodies (Muriithi *et al.,* 2015) .The observed increase in WBC count in this study is a physiological response to the presence of the extract in the system and also showed that the extract has immune boosting properties which is in line with the reports of Jorum *et al*. (2016).

Conclusion

In conclusion the present study showed that oral administration of methanol extract of *F. Capensis* leaf in normal rats resulted to a significant increase in the levels of erythrocytic parameters. This may suggest that the plant possess erythropoietin stimulating activity that also improve hematopoietic activity of the cells and the improvement in erythrocyte membrane integrity, thereby reducing haemolysis hence can play a vital role in management and prevention of anemia. This study also confirms and support that the plant possesses lipid lowering and anticoagulant activity which can be exploited in the management of cardiovascular disease and blood coagulation disorders. Further in vivo studies are required to elucidate the mechanisms by which the anticoagulant components of the plant affect their activity.

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