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Hypolipidemic Potentials of Aqueous Leaf Extract of Cape Fig (*Ficus capensis thunb*) in High Fat Diet-Induced Hyperlipidemic Rats

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ABSTRACT

Nature has been a source of medicinal agents for thousands of years and an impressive number of modern drugs have been isolated from natural sources, mainly based on their use in traditional medicines. The study was carried out to evaluate the hypolipidemic potentials of *Ficus capensis thunb* in high fat diet-induced hyperlipidemic rats. Twenty-five (25) Wistar rats were used for this study and were grouped into five groups consisting of five animals. Hyperlipidemia was induced by feeding the rats with high fat diet for a period of four (4) weeks. The results from the phytochemical analysis of the plant revealed the presence of tannins, saponins, protein, xanthroprotein, anthraquinones, alkaloids, phenolic compound, flavonoids and cardiac glycosides. After a period of four weeks of feeding, hyperlipidemia was established judging from significant increase ($p<0.05$) in serum levels of TC-C, LDL-C and TG with a concomitant decrease in serum HDL levels as compared to normal rats. Treatment with aqueous leaf extract of *Ficus capensis* at a doses of 200, 400 mg/kg b.w and also with simvastatin at a dose of 10 mg/kg b.w orally for 28 day significantly ($p<0.05$) decreased the serum levels of TC, TG and LDL accompanied by an increase in serum level of HDL as compared with those of the hyperlipidemic group. The liver tissues of hyperlipidemic group were characterized by fat accumulation, vascular congestion, cords disorder, and infiltration of inflammatory cells. Aqueous leaf extract of *Ficus capensis* mitigated both the elevated serum lipid and histological abnormalities.

Keywords: Hyperlipidemia, High fat diet, *Ficus capensis thumb*, Cholesterol.

Introduction

Hyperlipidemia is a disorder of a lipoprotein metabolism that is often identified by elevated serum low-density lipoprotein (LDL) accompanied by low serum high-density lipoprotein (HDL). This disease condition is due to excess lipids particularly triglycerides and cholesterol in the blood.[1,2] It is the main cause of cardiovascular diseases and according to American Heart Association, it is the leading global cause of death, accounting for more than 17.3 million deaths per year and this number is presumed to grow to more than 23.6 million by 2030.[3] In Nigeria , death rates of 16.1%, 6.5% and 12% were estimated for hyperlipedemia, obesity and cardiovascular diseases (CVD) respectively.[4,5] This could be as a result of over indulgence of cholesterol and alcohol rich foods, sedentary life style, age and stress.[6,7] Decline in HDL receptors could also lead to accumulations of LDL - cholesterol and thus promoting its oxidation in the blood that ultimately leads to atherosclerosis.[8] Studies have shown that cholesterol fed rats produce a higher concentration of superoxide in a reaction catalyzed by NADP dependent oxidase activity in the hearts.[9] This caused increased lipid peroxidation since the heart antioxidant enzymes are also concomitantly decreased in this condition.[10] Lipid peroxidation has been implicated in pathogenesis of inflammation of the vascular tissues, endothelial injury and subsequently leads to the development of atherosclerosis.[11,12] Reducing the blood LDL levels as well as increasing HDL levels in blood might be a reasonable goal for chemotherapy of hyperlipidemia.

Although most common synthetic drugs such as statins, nicotinic acid derivatives, bile acid binding resins and cholesterol absorption inhibitors used in the treatment of hyperlipidemia might be effective in lowering cholesterol, they are often scarce and expensive.[13] Itching, constipation, nausea, vomiting, headache and dizziness are some of the common contra-indications associated with these conventional drugs.[14,15] The toxicity associated with synthetic drugs coupled with the high mortality and morbidity of hyperlipidemia and the potency of natural product from plants have captivated our interest to search for an effective and alternative treatment for hyperlipidemia from medicinal plants. *Ficus capensis* (family: Moraceae) is a wild plant which has been found to be useful in traditional medicine because it exudes latex in all its parts.[16] Feleke *et al.*, in 2005 reported that the latex has phytochemicals (Ursine and Oleannatri terpenoids) that may be effective in cancer treatment.[17] Methanolic extract of its roots is potentially effective against chloroquine resistance malaria. The fruits are used to make food preservative and it is also edible in fresh or dried form.[18] The latex is used to treat ulcer and gout while the leaves are used to treat dermatitis. Latex of *Ficus racemose* is used as aphrodisiac and bark powder is used to treat diabetes, ulcers and the fruits are used as laxatives. The fruits and leaves of *Ficus carica*

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shows spasmolytic activity mediated through the activation of k^+-ATP channels along with anti-platelet activity.[19]

Materials and Methods

Collection and identification of plant

The wild plant studied was *Ficus capensis thunb.* The plant was harvested from a farm in Oyigbo Local Government Area of Rivers State, South-South of Nigeria in August, 2019. After harvest, the plant was taken to the Herbarium Unit Department of Plant Science, University of Port Harcourt, Nigeria, for identification and authentication. A voucher specimen of the collected sample was deposited in the institutional herbarium for future reference. Reference no: UPH/PSB/2018/043.

Preparation of leaf samples

The stalks of the plants were removed and the leaves rinsed with distilled water, kept in cool condition until all the water droplets have evaporated. The leaves were air dried for a period of two weeks after which they were blended to powder using a blender. The sample was packed in an air-tight container and preserved in a refrigerator for analysis.

Preparation of extract

A portion of 230g of the powdered plant was macerated in a distilled water for a period of twenty four hours. The extract was filtered by Whatman No.1 filter paper and the filtrate was evaporated under a pressure by using rotary evaporator .A glass funnel was placed on a retort stand to filter the sample using a Whatman (No. 1) filter paper. The filtrate was allowed for 1-2 hours to observe any residue or sediment. The clear filtrate was put in a rotatory evaporator which separated the water from the extract leaving the extract in a paste form. The extract was poured in a crucible plate for drying on a steam bath at 40˚c and 50^{o}C since it is an aqueous extract. The yield of the crude extract measured with an analytical balance was 25 g which was later stored in a refrigerator pending its usage.

Experimental animals

A total of twenty-five (25) wistar rats of both sexes weighing 120-150 g were purchased from animal house of Department of Biochemistry, University of Port Harcourt and kept in well aerated cages in the animal house. The animals were allowed to acclimatize for a period of two weeks before the commencement of the experiment. They were fed with rat chow and water at *ad libitum* (Guinea Feed Ltd. Nigeria) and water *ad libitum*.

Induction of hyperlipidemia

Hyperlipidemia was induced by feeding the rats with high fat diet (60% of normal feed, 30% of lard and 10% of sucrose) for a period of four (4) weeks. Hyperlipidemia was confirmed after four (4) weeks on blood samples taken via the tail of the rats for lipid profile analysis.

Experimental design

A total of twenty five adult Wistar rats were used in this study. They were divided into five groups with each group consisting of five rats.
Group I: (Normal control) received only 1 mL distilled water daily for a period of 28 days.
Group II: (Hyperlipidemic rats control) received only 1 mL distilled water daily for a period of 28days
Group III: (Hyperlipidemic rats and standard drug) received simvastatin at a dose of 10 mg/kg b.w orally for a period of 28 days
Group IV: (Hyperlipidemic rats and extract) received aqueous leaf extract of *Ficus capensis* aqueous at a dose of 200 mg/kg b.w orally for a period of 28 days
Group V**:** (Hyperlipidemic rats and extract) received aqueous leaf extract of *Ficus capensis* aqueous at a dose of 400 mg/kg b.w orally for a period of 28 days

Blood collection and serum preparation from rats

The rats were fasted overnight after the last treatment and then anesthetized with chloroform. The blood was collected via cardiac puncture in the sample tube using syringe. The sera obtained from Blood collected after centrifugation at 4500 rpm for 5 min was used to analyze lipid profiles.

Lipid profile analysis

Serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) were determined by enzymatic methods with commercial test kits (Randox Laboratories, Crumlin, England). The low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald *et al.,* (1972) formula, LDL-C = TC - (HDL-C + VLDL-C).[20] Atherogenic index was derived using the formula:

Atherogenic Index (AI) = LDL-C /HDL-C

Qualitative analysis of phytochemicals

Qualitative phytochemical constituents were determined using standard methods.[21]

Histopathology of the liver

Animal liver from each group were preserved in 10% neutral buffered formalin solution for 24 h and washed with 70% ethanol. Tissues were then placed in small metal caskets, stirred by a magnetic stirrer, dehydrated using alcohol series from 70% to 100% alcohol and embedded in paraffin using an embedding machine. Paraffin blocks were sectioned using a rotary ultra-microtome, distributed onto glass slides and then dried overnight. Slides were observed under a light microscope after being stained with hematoxylin and eosin (H&E) dyes and mounted.[22] Capture and scoring for morphological changes were done by a pathologist blind to the treatments at the Pathology Unit, University of Port Harcourt Teaching Hospital.

Statistical analysis

Statistical analysis for experimental groups was performed using one-way analysis of variance (ANOVA). Differences between groups were determined by Duncan multiple and P value ≤ 0.05 was considered statistically significant. All data were expressed as Means ± standard error of means (SEM).

Results and Discussion

Preliminary qualitative phytochemical analysis of Ficus capensisleaves

The qualitative phytochemical analysis of *Ficus capensis* leaves are shown on Table 1 below.

Table 1: Preliminary qualitative phytochemical analysis of *Ficus capensis* leaves

Secondary metabolites	Result
Alkaloids	+
phenolic compounds	+
Flavonoids	+
Saponins	+
Coumarins	-
Tannins	+
Quinines	-
Anthraquinones	+
Proteins	+
Xanthroproteins	+
Steroids	-
cardiac glycosides	+

Note: +: present, -: absent.

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Qualitative phytochemical analysis highlighted the presence of alkaloids, flavonoids, phenolic compounds, saponins, tannins, anthroquinones, proptein, xanthroprotein and cardiac glycosides. Results revealed that coumarin, quinine and steroid were absent.

The result from the phytochemical study revealed the present of alkaloids, flavonoids, saponins, tannins, Anthraquinones, Proteins, Xanthroproteins and cardiac glycosides as the major phytochemicals in the plant sample. Also, the results from the rats fed with high fat show significant ($p < 0.05$) increases in serum levels of TC, TG and LDL accompanied by a reduction of serum level of HDL though not significant ($p > 0.05$) as compared with those of the normal group .There was also significant ($p < 0.05$) increase in ratio of LDL to HDL compared with those of the normal group. Treatment with aqueous leaf extract of *Ficus capensis* at doses of 200, 400mg/kgbw and also with simvastatin at a dose of 10mg/kgbw orally for a period of 28day significantly ($p < 0.05$) decreased the serum levels of TC, TG and LDL accompanied by an increases in serum level of HDL as compared with those of the hyperlipidemic group. There was also significant ($p < 0.05$) decrease in ratio of LDL to HDL as compared with those of the hyperlipidemic group. The qualitative phytochemical analysis carried out on the powdered leaf of *Ficus capensis thunb* revealed the presence of tannins, saponins, protein, xanthroprotein, anthraquinones, alkaloids, phenolic compound, flavonoids and cardiac glycosides as the major phytochemicals present in the plant. The presence of these secondary metabolites may justify their usage as anti-inflammatory, anti-antioxidant agents and astringents against diarrhea as these properties are attributed to flavonoids and tannins respectively.[23] The presence of saponin might also suggests its usage as an antimicrobial agent since saponin protect plants from microbial pathogens.[24] Secondary metabolites are reported to have lots of biological and therapeutic properties therefore the plant is expected to have many medicinal uses.[25]

In the study, administration of high fat diet to rats for a period of four weeks led to hyperlipidemia judging from significant increase ($p < 0.05$) in serum levels of TC-C, LDL-C and TG with a concomitant decrease in serum HDL levels as compared to normal rats. There was also significant increase ($p < 0.05$) in atherogenic index as compared to normal rats. The observed effects might be due the ability of high-fat diet to activate biosynthesis of the lipid in the liver with a consequent increase LDL-C in the blood which in turn leads to oxidative stress by increasing the production of reactive oxygen species which is usually accompanied by reduction of antioxidant enzymes. Studies have shown that this process is associated with the development of metabolic syndromes such as atherosclerosis, diabetes mellitus and hypertension. Treatment with aqueous leaf extract of *Ficus capensis* at doses of 200, 400mg/kg b.w and also with simvastatin at a dose of 10mg/kgbw orally for a period of 28days significantly ($p < 0.05$) decreased the serum levels of TC, TG and LDL accompanied by an increases in serum level of HDL as compared with those of the hyperlipidemic group. There was also significant ($p < 0.05$) decrease in atherogenic index as compared with those of the hyperlipidemic group. Hypolipidemic effect *of Ficus capensis mig*ht be due to its ability to alter the gene expression and activity of enzymes involved in lipid metabolism. Though the exact mechanism of the *Ficus capensis is unknown*, studies have shown that up regulation of the genes coding for the enzymes cholesterol 7α-hydroxylase , liver X receptor alpha , and peroxisome proliferation activated receptor-α will enhance the production of bile acid and its removal whereas down regulation of the expression gene encoding for 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) and sterol-responsive element binding protein-2 (SREBP2) will lead to inhibition of biosynthesis of cholesterol. Hypolipidemic effect of *Ficus capensis might* also be due to its ability to up regulate the low-density lipoprotein receptor (LDLR) leading to inhibition of liver biosynthesis of cholesterol.[26]

Histological examination of liver sections of normal rats shows an intact structure that consist of normal nucleus, abundant cytoplasm and central vein whereas there were morphological alterations in tissue of liver of the rats fed with high fat diet. In fact the tissue was characterized with fat accumulation, vascular congestion, cords disorder, and infiltration of inflammatory cells. Treatment with aqueous leaf extract *Ficus capensis* at a doses of 200, 400 mg/kg b.w and also with simvastatin at a dose of 10 mg/kgbw orally for a period of 28day significantly mitigated the pathological alternations to nearly normal features.

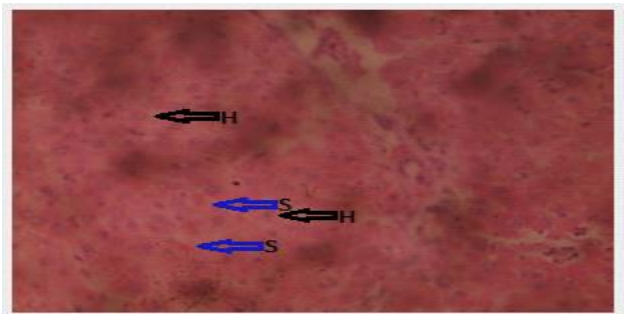

Plate 1: Photomicrograph of the liver of normal control group (H&E X400). Result shows a normal liver histology

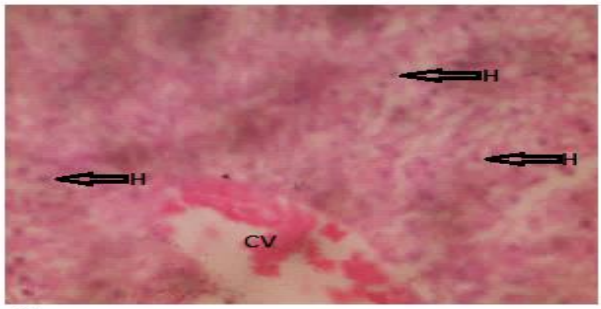

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Plate 2: Photomicrograph of HFD control group not treated (H&E X400). Result shows abnormal hepatocytes, a congested central vein is also seen.

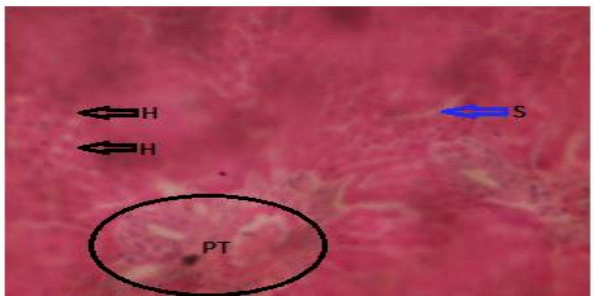

Plate 3: Photomicrograph of liver tissue of HFD + simvastatin extract treatment for 14 days (H&E X400). Result shows a normal liver histology.

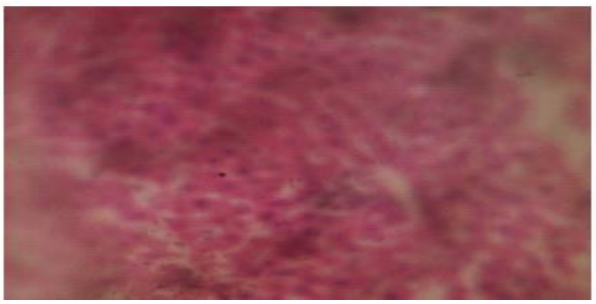

Plate 4: Photomicrograph of liver tissue of HFD + 200 mg/kg bw extract treatment for 14 days (H&E X400). Result shows a normal liver histology.

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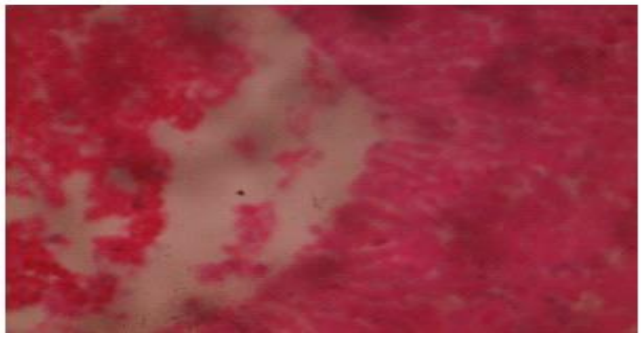

Plate 5: Photomicrograph of liver tissue of HFD + 400 mg/kg bw extract treatment for 14 days (H&E X400). Result shows a normal liver histology.

Conclusion

The study revealed that feeding wistar rats with high fat diet for a period 28days lead to hyperlipidemia. Aqueous leaf extract of *Ficus capensis* mitigated both the elevated serum lipid and histological abnormalities. Research is in progress to unfold both hypolipidemic effects and mechanism of action of the extract.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Table 2: Result of Lipid Profile of Normal and Treated Groups of High Fat Diet- Induced Hyperlipidemic Rats

Parameter	TC mg/dL	TG mg/dL	HDL mg/dL	LDL mg/dL	LDL-C/HDL	TC/HDL
Group I	117 ± 2.3b	109.5b ± 3.51	23.4 ± 0.06	72.93 ± 0.12b	3.12 ± 1.3	5.0 ± 0.5
Group II	141.6 ± 3.51a[b]	157.5 ± 3.51a[b]	20.2 ± 0.06[a]	102.57 ± 0.09a	5.1 ± 2.3[a]	7.01 ± 0.9
Group III	122.46 ± 4.68b	108.6 ± 2.73b	20.28 ± 0.05b	80.34 ± 0.06b	3.9 ±1.8[b]	6.03 ± 0.4
Group IV	123.24 ± 2.7b	121 ± 1.95[ab]	21.1 ± 0.05b	78.78 ± 0.07b	3.7 ± 1.6[b]	5.8 ± 0.6
Group TC	115.1 ± 2.34b	120.1 ± 1.17[ab]	23.4 ± 0.04b	68.25 ± 0.10b	2.9 ± 1.2[b]	4.9 ± 0.3

The data was expressed as Means ± standard error of means (SEM)
[a]$p < 0.05$ significantly different from the control group (group I)
[b]$p < 0.05$ significantly different from the hyperlipidemic control group (group II)

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