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FICUS GLUMOSA DELILE LEAF EXTRACT ATTENUATES SOME BIOCHEMICAL MARKERS IN TESTOSTERONE-INDUCED BENIGN PROSTATIC HYPERPLASIA IN WISTAR RATS.

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ABSTRACT

Ficus glumosa is used extensively in traditional medicine to manage and remedy some health conditions. This study evaluated the impact of *F. glumosa* leaf extract on selected biochemical indices of testosterone-induced benign prostatic hyperplasia in male Wistar rats. Thirty-six male rats were randomly divided into six groups (n = 6). Rats in the Normal Control (NC) received feed without any special treatment, rats in the Benign Prostatic Hyperplasia Control (BPHC) group were administered 50 mg/Kg body weight testosterone, rats in the Standard Control (STDC) group received 50 mg/Kg body weight testosterone + 5 mg/Kg body weight finasteride, rats in the low dose (LD) group received 50 mg/Kg body weight testosterone + 100 mg/Kg body weight of *F. glumosa* extract, rats in the medium dose group received 50 mg/Kg body weight testosterone + 200 mg/Kg body weight of *F. glumosa* extract, rats in the high dose group received 50 mg/Kg body weight testosterone + 400 mg/Kg body weight of *F. glumosa* extract. The animals received water and feed *ad libitum* for 28 days. They were anaesthetized (after treatment period) using ketamine hypochlorite. Blood samples were collected, centrifuged and serum harvested for analyses using standard methods and one way ANOVA followed by least square difference (LSD) post-hoc comparison test. Results indicated a significant decrease at $p< 0.05$ in serum electrolytes (Na and Cl) in the groups treated with *F. glumosa* extract when compared to the control groups. The serum urea, uric acid and creatinine levels of the groups treated with 200 mg/kg b.w and 400 mg/kg bw of *F. glumosa* leaf extract decreased significantly when compared to the BPHC standard and normal control groups. Also the serum level of aspartate aminotransferase indicated similar trend. We therefore conclude that *F. glumosa* leaf extract may attenuate some biochemical indices especially serum electrolytes (Na and Cl), aspartate aminotransferase as well as HDL-c level in testosterone – induced benign prostatic hyperplasia in Wistar rats.

KEYWORD: *Ficus glumosa,* benign prostatic hyperplasia and biochemical indices.
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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a progressive noncancerous enlargement of the epithelial cells and smooth muscle of the prostate gland accompanied by lower urinary tract symptoms [Pearson and Kashiefi 2008]. The enlargement of the prostate compresses the urethra, thus restricting flow of urine from the bladder. The prevalence of BPH is age dependent with approximately 50 % of men developing BPH-related symptoms at 50 years of age but the condition is not common before age 40. At the age of 85, the prevalence is as high as 95 % and 20-30 % of men at the age of 80 years require surgical intervention to manage BPH [Pearson and Kashiefi 2008, Berry *et al*., 1984] The prevalence of bothersome symptoms, just like the histologic evidence increases with age. Moderate to severe lower urinary tract symptoms have been reported on half of the men who have histologic diagnosis of BPH. Risks of developing morbidities and complications are currently unclear as data on population based studies has only been availed recently. Currently, there is no specific time frame at which a certain symptom complex develops to complete

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urine retention [Madersbacher 2004]. Serious BPH-related complications are uncommon and BPH-related mortality is rare.

Several mechanisms seem to be involved in the development of and progression of BPH and thus the etiology still remains uncertain in some aspects. The BPH is caused by increased growth of the prostate gland and increased smooth muscle tone of the prostate [Azadzoi 2003]. Dihydrotestosterone (DHT), a metabolite of testosterone is the main mediator of prostate growth. Dihydrotestosterone is formed by breakdown of testosterone by 5-alpha reductase enzyme in the prostate cell [Lansky 2008]. The enzyme is the target for drug therapy aimed at reducing the size of the prostate. The method to be used for management of BPH patients depends on the progression of the condition and whether the symptoms affect the quality of life of patients. BPH patients with symptoms that do not bother them to need surgical or drug intervention are advised to undergo watchful waiting [McConnell *et al*., 2003]. Watchful waiting involves education and lifestyles modification, periodic monitoring to establish the severity of lower urinary tract symptoms (LUTS), weight loss and increase physical activity to decrease risk factors and reduce symptoms associated with BPH [McConnell *et al*., 2003].

Since ancient times, Ficus species has been a well-tolerated effective traditional medicine for the treatment of disease in Nigeria and beyond. Most of the species of Ficus are used as vegetables in soups consumed as local delicacies (Obiabang et al., 2018). The anticancer activity of Ficus glumosa has been reported and its activity has been linked to the presence of the secondary metabolic profile (polyphenols(Ibrahim et al,.2017, Barde and Musa 2019). It is reported that the roots, stem bark or wood, branches, fruit pulp, peel, leaves, and seeds of different species of Ficus plant contain the flavonoids and phenolic compounds as major phytochemical components along with polyphenol, polysterols and triterpenoids.(Most of these phytochemical compounds show health promoting effects in human due to their strong antioxidant potential. On the basis of their phytochemical composition and antioxidant profile, they have been found to show several biological activities. The studied species of Ficus plants were found to possess anticancer, hepatoprotective, hypoglycemic, antitumor, antioxidant, anthelmintic, analgesic, antimicrobial activity, anti-parasitic, hypolipidemic, anti-inflammatory, antibacterial, anti-ulcerogenic, mucoprotective, gastroprotective, antifungal, antiviral, antimalarial, and antiparasitic activities [Abdel-Hameed *et al.*, 2014, Suryati 2011]. Higher concentrations of phytochemicals are responsible for the strong antioxidant potential of plants of genus Ficus and are helpful in the prevention of certain cardiovascular, neurodegenerative, and hepatic diseases caused by oxidative stress [Gregory 2009]. Obi-abang *et al*. (2020) investigated the ameliorative effects of *Ficus glumosa* leaves on some biomarkers of kerosene toxicity in Wistar rat model. This study was aimed at investigating the effect of *Ficus glumosa* leaves on testosterone induced BPH in male Wistar rats.

MATERIALS AND METHODS

Materials

The testosterone and other drugs used for this study were purchased from Bez pharmacy, Etta-Agbor road, Calabar, Cross River State, Nigeria. Chemical kits were purchased from Sigma.

Plant collection, identification and preparation

Ficus glumosa leaves were harvested from the campus of Cross River University of Technology (CRUTECH) Calabar. The plant with an assigned voucher number of BOT/FG/2015/1 deposited in the herbarium was previously identified by Mr. Frank Apojeye (Botanist} of the Department of Botany, University of Calabar. Thereafter, the leaves were thoroughly washed, shade dried at 25ºC for two weeks and subsequently ground into fine powder using a manual blender. The powdered sample was soaked in ethanol solvent for two days, it was filtered with chess cloth and the filtrate was dried using rotary evaporator. The extract obtained was stored in a refrigerator at 4^{o} C using an air-tight plain tubes until when required for administration.

Experimental animals

A total of thirty-six male rats (weighing 60-80 g) were obtained from the animal house of the Department of Biochemistry, University of Calabar. Prior to the start of the experiment, the animals were allowed to acclimatise in well-ventilated standard cages with iron mesh doors for 21 days. In the course of the 28-day experimental duration, the rats were exposed to a 12-hour light/dark cycles under humid tropical conditions allowed access to grower's mash (rat chow) and clean tap water ad libitum. The animal room used for this study was well ventilated and maintained at a temperature range of 27^{o} C – 37^{o} C. The experimental procedure employed for this study was approved by the Institutional Animal Ethics Committee.

Experimental design

Thirty- six male rats were divided randomly into six groups (n = 6). All the experimental groups except the normal control were induced benign prostatic hyperplasia (50 mg/Kg body weight). Rats in the Normal Control (NC) group received only feed without any special treatment, rats in the Benign Prostatic Hyperplasia Control (BPHC) group were administered 50 mg/Kg body weight testosterone, rats in the Standard Control (STDC) group received 50 mg/Kg body weight testosterone + 5 mg/Kg body weight finasteride, rats in the low dose (LD) group received 50 mg/Kg body weight testosterone + 100 mg/Kg body weight of *F. glumosa* extract, rats in the medium dose group received 50 mg/Kg body weight testosterone + 200 mg/Kg body weight of *F. glumosa* extract, rats in the high dose group were administered 50 mg/Kg body weight testosterone + 400 mg/Kg body weight of *F. glumosa* extract. The animals in all the groups were allowed access to water and feed *ad libitum* for 28 days. Measurements of feed intake were taken daily while that of body weights was carried out on weekly basis.

BIOCHEMICAL ANALYSES

Estimation of markers of hepatic function

Activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) in serum were determined based on earlier reports by [Sedlak, and Lindsay, 1968] using spectrophotometry assay kits (Randox Laboratory, United Kingdom). Total bilirubin, conjugated bilirubin and unconjugated bilirubin were estimated spectrophotometrically [Murray *et al*., 2004]

Estimation of markers of renal function

Serum concentrations of urea, uric acid, creatinine, albumin, globulin and total proteins were evaluated using Randox assay kits (Randox Laboratory, United Kingdom). The concentrations of Na^+, and CL^- in the serum were assayed using Agappe assay kit (Agappe diagnostics, India). An automatic analyser ROCHE module Cobas 6000 (C-501 and C-601) (Roche diagnostics, North America) was employed for this analysis.

Estimation of serum lipid indices

Serum concentrations of total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and triglyceride (TG) were assayed with spectrophotometric assay kits (Sigma-Aldrich, USA) [Allain *et al*., 1974, Assmann *et al* 1983 and Sullivan *et al*., 1985]. Low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C) levels in the serum were estimated based on previously described by Friedewald *et al.*, 1974 where LDL-c = (Total cholesterol – HDL-c – TG)/5.

Statistical analysis

The data are presented as mean ± SEM (n = 6). Data obtained were analysed using one-way ANOVA followed by least square difference (LSD) post-hoc comparison test to evaluate significant difference between the mean values of the experimental and control groups. Differences at $P < 0.05$ were regarded as significant. Graphpad prism version 7 and SPSS software package version 23.0 were used for the statistical analyses.

Results

Effect of *F. glumosa* leaf extract on some markers of hepatic function

The outcome of the 28- day administration of *F. glumosa* leaf extract on serum activity of AST, ALP and ALT are presented in *figure 1*. The results revealed significantly ($p < 0.05$) raised levels of AST and a slight elevation of ALP which was not statistically significant at ($p > 0.05$). compared to the NC group, the BPHC group upon treatment with standard drug and *F. glumosa* leaf extract, a decline in serum levels of AST and ALP when compared to the untreated group and NC. There was no significant change observed for serum concentrations of total bilirubin, direct bilirubin and indirect bilirubin as presented in *figure 2*.

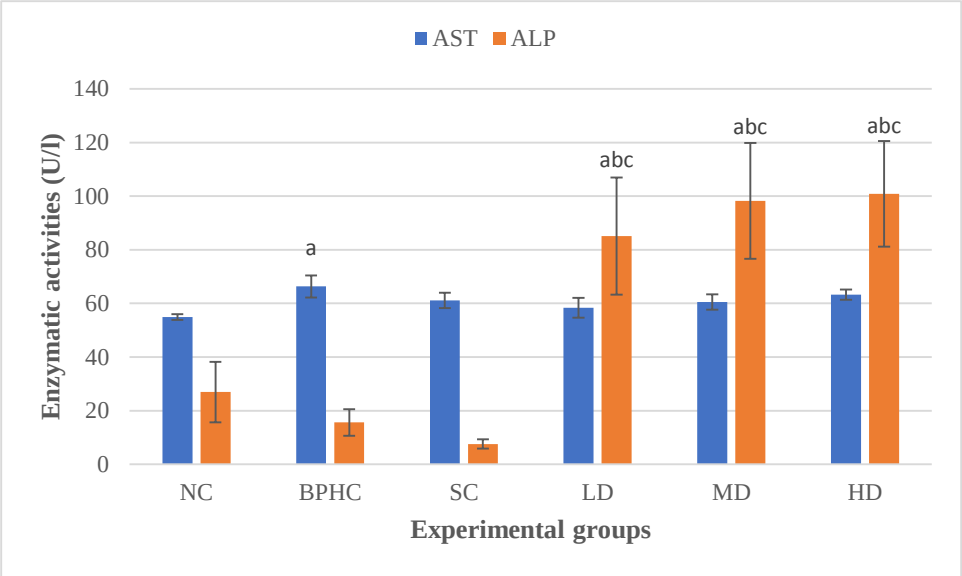

Figure 1: effect of F. glumosa leaf extract on serum levels of AST and ALP

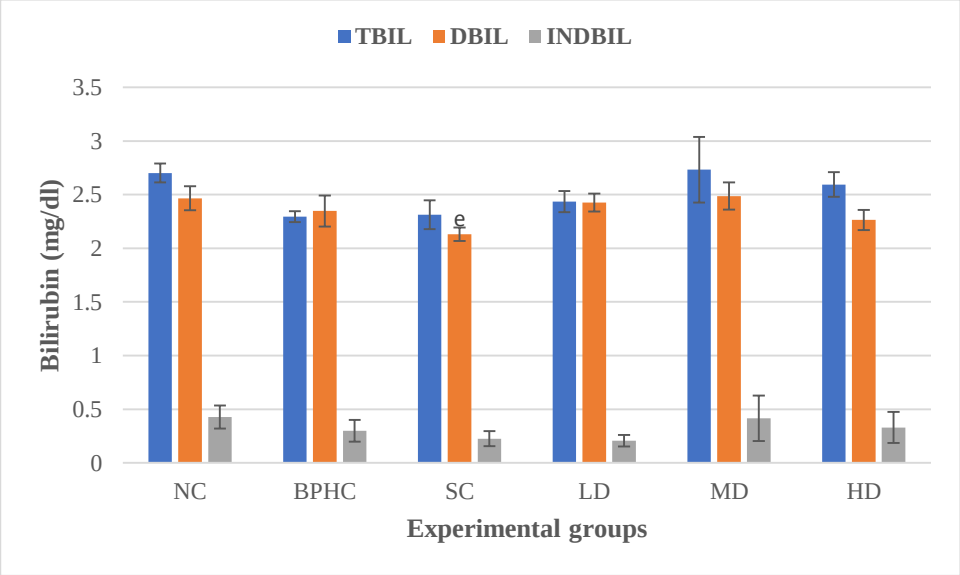

Figure 2: Effect of *F. glumosa* leaf extract on serum levels of total, direct and indirect bililrubin

Effect of *F. glumosa* leaf extract on some markers of renal function

As shown in *figure 3*, there was a decrease in serum urea level that was significant at p>0.05 in the BPHC group relative to the NC. Following treatment with extracts, serum urea concentration was observed to decrease significantly when compared to the controls. Furthermore, uric acid concentration was slightly elevated in the BPHC untreated group compared to the NC. Although the finasteride treated group, SC caused a non significant decrease compared to the NC and BPHC groups, The extract treated groups showed raised uric acid level except in the 200 mg/kg b.w treated group relative to NC. There was no significant change was in the serum concentration of creatinine following treatment with standard drug and extract doses.

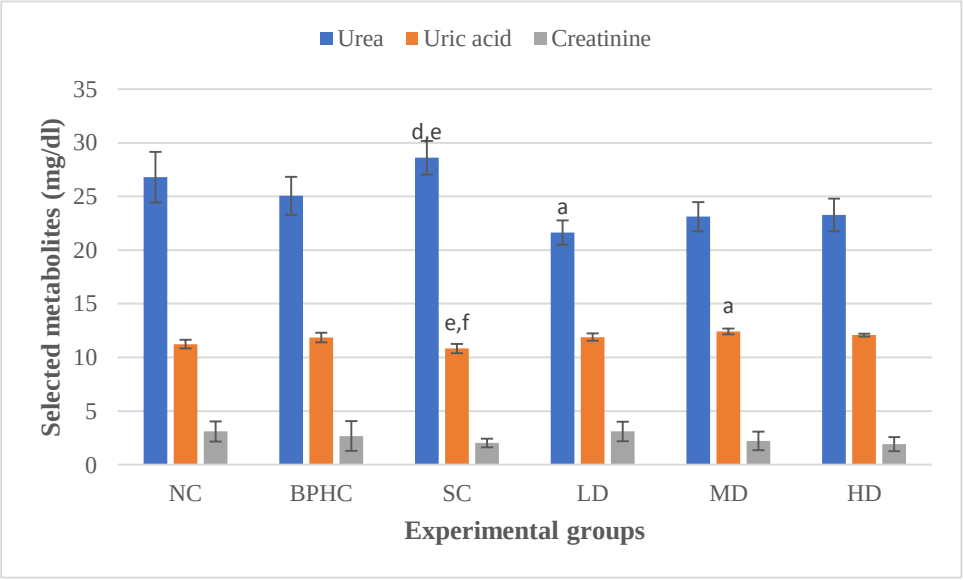

Figure 3: Effect of *F. glumosa* leaf extract on serum levels of urea, uric and creatinine

Additionally, the results observed for the effect of 28 -day treatment on total proteins is presented in *figure 4*. The untreated group, BPHC showed a raised concentration of total proteins that was not significant when compared to the NC. However, apart from the group treated with 400 mg/kg b.w of *F. glumosa* leaf extract that presented a slightly elevated level of total protein, all treated groups showed a decrease in total protein level compared to the NC and BPHC, although this observation was not significant at (p<0.05). There was no observed significant change in serum albumin concentration in the untreated BPHC group relative to NC while treatment with all extract doses resulted in an insignificant (p<0.05) raised albumin level compared to NC and BPHC. There was no observed change in globulin levels in all experimental groups.

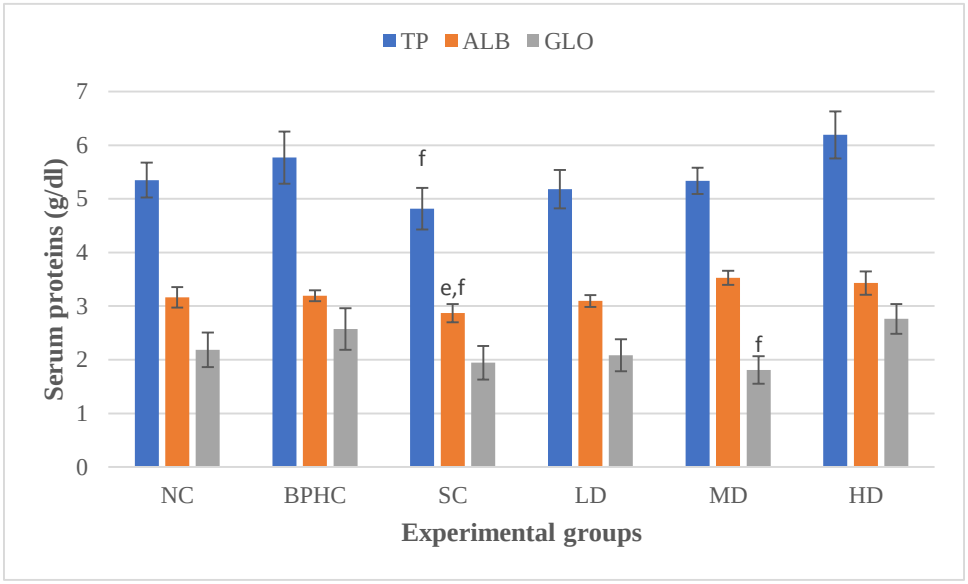

Figure 4: Effect of *F. glumosa* leaf extract on serum levels of total proteins, albumin and globulin

The serum concentration of electrolytes as presented in *figure 5*, while the BPHC slightly raised Na levels compared to the NC, treatment with the standard drug, SC and doses of *F. glumosa* extract decreased Na levels compared to NC and BPHC, with a significant ($p<0.05$) decline observed for the 200 mg/kg b.w group. There was no significant change observed in serum chloride level following treatment. Also similar pattern was observed for the K^+ levels, although treatment with standard, SC and extract doses showed an elevated trend compared to NC and BPHC with the 100 mg/kg b.w and 200 mg/kg bw treated groups indicated higher levels.

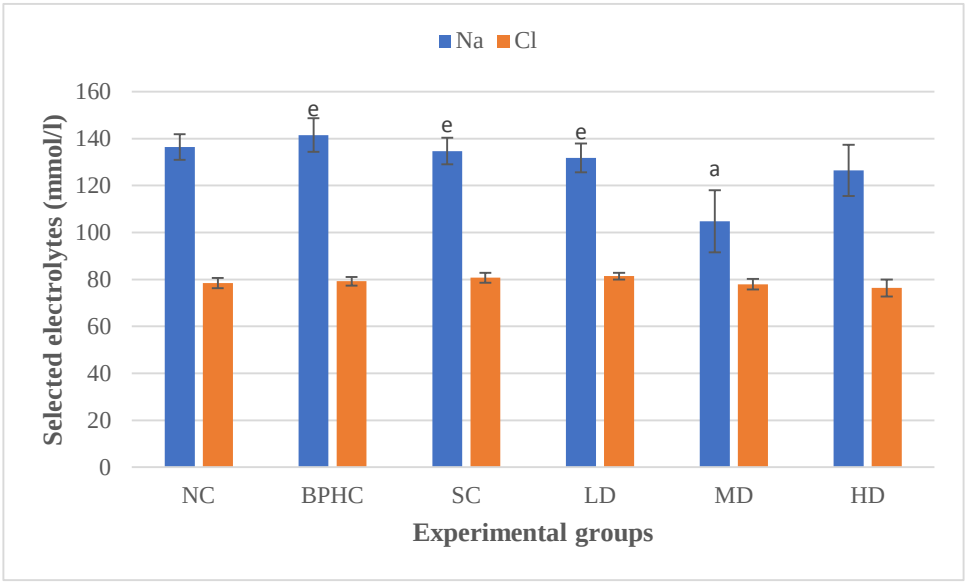

Figure 5: effect of *F. glumosa* leaf extract on serum levels of sodium and chloride

Effect of *F. glumosa* leaf extract on serum lipid profile

The effect of *F glumosa* on serum lipid profile in untreated and treated experimental groups is presented in *figures 6 and 7* respectively. In comparison to the NC group, TC concentration in the serum decreased in the untreated BPHC group, while it was observed to decrease in the SC group relative to BPHC, treatment with the 100 mg/kg b.w and 400 mg/kg b.w extract doses showed raised levels. However, it was observed that treatment with the 200 mg/kg b.w extract dose showed a significant ($p<0.05$) decline in TC concentration compared to NC and BPHC. Although the concentration of TAG decreased across treated and untreated groups relative to NC, when compared to BPHC group, treatment with *F. glumosa* leaf extract caused a non-significant ($p>0.05$) increase in TAG levels compared to BPHC. The HD-c, indicated a significant ($p<0.05$) decrease in the BPHC group when compared to NC. Interestingly, treatment with finasteride in the SC group as well as the 200 mg/kg b.w and 400 mg/kg b.w of *F. glumosa* leaf extract caused a marked increase in the level of HDLc compared to BPHC.

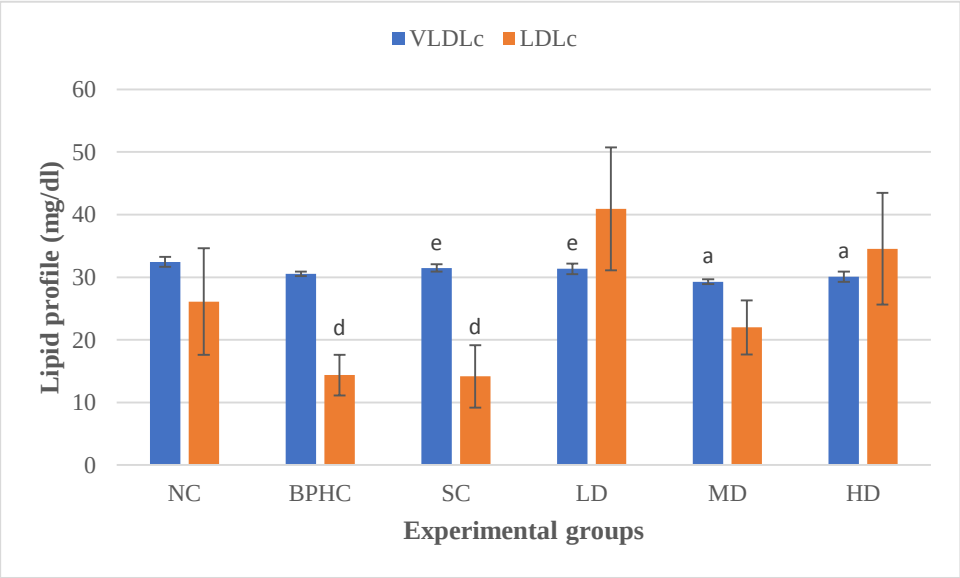

Figure 6: Effect of *F. glumosa* leaf extract on serum levels of total cholesterol, triacylglycerol and high densitylipoprotein-cholesterol

The serum concentration of VLDLc (*figure 7*) was observed to decrease in the untreated BPHC group compared to NC while all treatment groups including SC showed no difference in VLDLc compared to BPHC but significantly declined in the MD and HD extract treated groups compared to NC. The concentration of LDLc decreased in BPHC group compared to NC. Treatment with the standard drug, SC showed no significant difference compared to BPHC but when compared to NC, a decline was observed. Treatment with *F. glumosa* extract caused a significant ($p<0.05$) increase in LDLc in both the LD and HD groups relative to NC and BPHC while the result from MD group revealed a decrease in LDLc concentration compared to NC. This observation was not significant ($p> 0.05$).

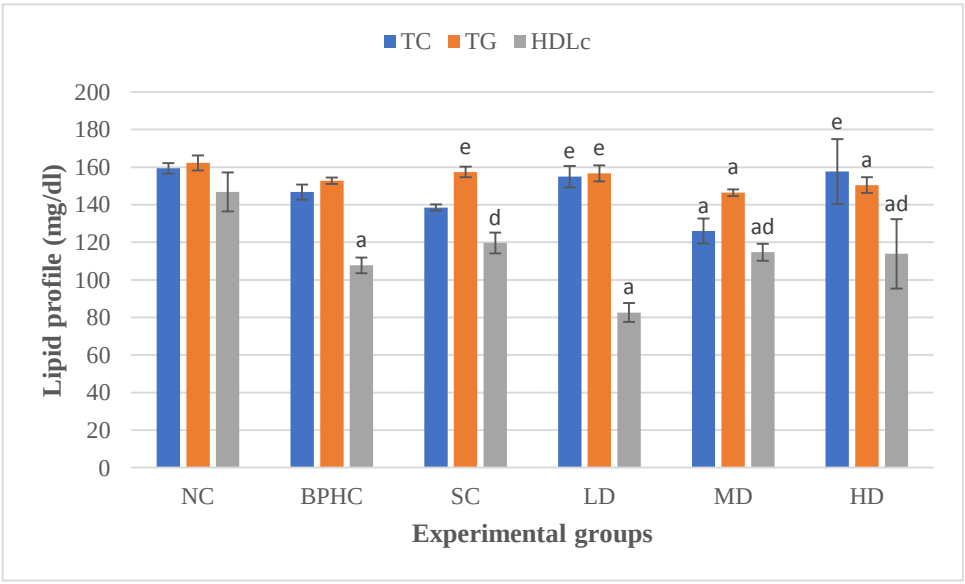

Figure 7: effect of *F. glumosa* leaf extract on serum levels of very low density lipoprotein-cholesterol and low density lipoprotein-cholesterol

DISCUSSION

The global burden of benign prostatic hyperplasia has been on the increase with statistics indicating that at age 60 more than half of the men have BPH while age 85 and above have a prevalence of 90% (Madersbacher *et al*., 2019). Serum enzymes and other biochemical markers (total protein, albumin, creatinine, uric acid and lipid indices) are tools used especially in the determination of hepatic and renal functions, however, in complications associated with benign prostatic hyperplasia these indices could be useful. In the present study, treatment with *F. glumosa* leaf extract indicated a statistically non-significant decrease at $p<0.05$ in serum levels of AST and ALP when compared to the BPHC untreated group and NC. This is in line with the findings of Ebenyi *et al.*, (2020). An increased ALP following BPH induction might have probably occured as a result of perfusion stimulated by renal and hepatic dysfunctions and inflammation associated with BPH disorders (Noriaki *et al.,* 2014). It equally implies that the extract did not exert probable ameliorative effect on the benign prostatic hyperplasia in Wistar rat models.

Plasma levels of Urea and Creatinine are indicators of kidney functions (Mohamed *et al.,* 2016). Results of this study showed that *F. glumosa* leaves decreased the serum concentration of Urea when compared to the SC, BPHC and NC gropus. No significant difference was observed in the concentration of Uric acid and serum chloride across the various groups. Although BPH is not a life-threatening condition, the impact of BPH on quality of life (Q.L) can be significant and should not be underestimated (Wasserman, 2006). The natural history and evolution of benign prostate enlargement ends up in urinary obstruction causing degradation of renal function over time (Wein *et al.*, 2007). In this study, a significant association between BPH and renal impairment was observed as indicated in the raised levels of urea and creatinine in the BPHC group. This is in line with the findings of Emeje *et al*. (2017). Although the difference in the creatinine levels amongst the groups were not statistically significant, even though creatinine levels may be a key player in chronic kidney disease and other kidney damage. According to Rule and Lieber (2005), obtaining a serum creatinine measurement may be an appropriate screening for renal disease unrelated to BPH. The decrease in urea levels in the groups treated with *F. glumosa* when compared to the BPHC group is an indication of kidney function improvement in BPH condition by *F. glumosa* leaves.

Lipid profile evaluation of the study indicated a marked relationship between BPH and lipid levels. This is consistent with the works of Ahmed *et al*. (2010). The concentrations of serum total cholesterol, triglyceride, VLDL cholesterol, VLDL cholesterol and LDL cholesterol of the groups treated with *F. glumosa* were almost at par with the BPHC group. A different trend was observed in the 200 mg/kg b.w and 400 mg/kg b.w of *F. glumosa* leaf extract that caused a marked increase in the level of HDLc compared to BPHC. Nandesha *et al*. (2008), found that total cholesterol and LDL- cholesterol were significantly higher and HDL-cholesterol was lower in BPH cases compared to normal controls. They reported that insulin had significant regression with cholesterol, TG, LDL-c and VLDL-c. Insulin is said to be involved in the pathogenesis of BPH though its action on sympathetic nerve activity, sex hormones and insulin-like growth factor axis, they also suggested that dyslipidemia in BPH occurs due to insulin resistance as well as insulin playing a role in promoting prostate growth.

Ficus glumosa is also known to contain various secondary metabolites like phenolics, therefore it is not out of place to speculate that some of the phytoconstituents are presumably responsible for imparting the anti-hyperlipidemeic properties.

The possible mechanism by which the extract exerted the increased levels of HDLc could be due to rich phenolics present in *Ficus glumosa* leaves that may have improved the antioxidant status of the benign prostatic hyperplasia Wistar rat model. Cardiac risk factors (higher LDl-c levels) have been linked with BPH pathogenesis as described in the cohort studies by Parsons *et al*., (2008). The implication of this finding is that the leaf extract exerted no probable ameliorative effect on the benign prostatic hyperplasia in Wistar rat models. Other markers such as urea, total protein, bilirubin, uric acid and lipid indices did not show any significant change except the 200 mg/kg b.w and 400 mg/kg b.w of *F. glumosa* leaf extract that caused a marked increase at $P<0.05$ in the level of HDL-c compared to BPHC. We therefore conclude that *F. glumosa* leaf extract may attenuate some biochemical indices especially serum electrolytes (Na and Cl), aspartate aminotransferase as well as HDL-c level in testosterone –induced benign prostatic hyperplasia in Wistar rats.

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