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Combined ethanol extract of *Spermacoce radiata* and *Hypselodelphyspoggeana* prevents renal damage and dyslipidemia in benign prostatic hyperplasia induced rats

Uroko Robert Ikechukwu*, Anyiam Paul Ndubuisi, Uhuo Emmanuel Nnaemeka, Ajah Obinna

Department of Biochemistry, College of Natural Science, Michael Okpara University of Agriculture, Umudike, P.M.B 7267, Umuahia, Abia State, Nigeria
***Email:** *ir.uroko@mouau.edu.ng*

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ABSTRACT

Background & Aim: A combined ethanol extract of *Spermacoce radiata* and *Hypselodelphyspoggeana* leaves are used for the treatment of benign prostatic hyperplasia, but there is no scientific data on its safety level and effects on vital organs and biochemical parameters. This study investigated the effects of a combined ethanol extract of *Spermacoce radiata* and *Hypselodelphyspoggeana* leaves (CESHL) on the lipid profile and kidney function of benign prostatic hyperplasia (BPH) induced rats.

Experimental: A total of 21 rats were used for the acute toxicity study, while 30 were randomly distributed into five groups comprising six rats each (n = 6) for the BPH study. Group 1 served as normal control, while group 2 was BPH control that received 5 mg/kg of testosterone propionate/day for 28 consecutive days without treatment. Groups 3 – 5 received 5 mg/kg of testosterone propionate/day for 28 days but after an hour, they treated with 5 mg/kg of finasteride, 200 and 600mg/kg of CESHL/day, respectively, for 28 days.

Results: The acute toxicity result of CESHL indicated no mortality or any sign of toxicity. Administration of the extract caused a significant reduction ($p<0.05$) of theprostate weight, triacylglycerol, cholesterol, low-density lipoprotein (LDL-C), urea and creatinine concentrations in the treated groups when compared to the BPH control. A significant increase ($P<0.05$) in High-Density Lipoprotein (HDL) concentration was observed in all treated groups when compared to the BPH control group. Histological outcomes of rats' kidneys corroborated these findings.

Recommended applications/industries: These results indicate that the combined extracts possess antilipidemic and nephroprotective effects, which might help in the management of complications that might arise during BPH.

1. Introduction

Benign prostatic hyperplasia (BPH) is one of the most common urological diseases in elderly men over 50 years of age, which is characterised by enlargement of the prostate, lower urinary tract symptoms and alterations in tissue histomorphology (Briganti *et al.*, 2009). In BPH, the prostate gland is enlarged due to an increase in stromal and epithelial cellular counts leading to many health challenges such as urinary retention, recurring urinary tract infection, urinary irritation, and possibly bladder stones (Iscaife *et al.*, 2018). If left untreated, the obstruction to urine flow due to BPH can also lead to acute renal failure that can even be life-threatening (Fox *et al.*, 2004). However, when BPH is discovered in its earlier stages, therisk of developing such complications is lower. The cause of BPH has been linked to excessive androgen hormones

such as testosterone and dihydrotestosterone (DHT) because of increased 5-alpha reductase activity (Ho and Habib, 2011). Serum hyperlipidemia may also act as a precursor to BPH onset and progression (Parsons *et al.*, 2008), being a crucial stage to many disorders exhibiting inflammation such as arthritis, cancer, cardiovascular diseases (CVD) and asthma (Serhan, 2005). However, maintaining normal serum lipid levels could avert BPH progression and the need for surgery (Lekili *et al.*, 2006). Currently, 5α-reductase inhibitors and α-blockers such as finasteride and terazosin are the main therapeutic drugs for BPH (Minutoli *et al.*, 2016). These drugs cause adverse effects such as hypotension, fatigue, ejaculation disorders, sexual dysfunction, and an increased risk of prostate fibrosis (Traish *et al.*, 2011). More attention has been channelled towards phytotherapy in terms of providing a more effective and safer treatment strategy for patients with BPH since they are less toxic than synthetic drugs.

Species of *Spermacoce radiate* (DC.) and Hypselodephyspoggeana have an impressive number of phytoconstituents with reported medicinal properties. In traditional medicine, the leaf preparations of *H. poggeana* (Family: *Marantaceae*) are used for the treatment of sores, headache and heart problems, whereas leaves of *S. Radiate* (Family: *rubiaceae*) are used traditionally for various ailments such as in treating conjunctivitis, gallstones, haemorrhoids and to relieve headache. It is also reported to be useful in reducing obesity andcontrolling diarrhoea and urinary infections (Vinayak *et al.*, 2013). Both plants have over the years proven to be very important plants in traditional medicine and are found almost everywhere as they adapt easily to various environmental conditions, which supports their relevance in this study. Hence, this study was aimed at evaluating the effects of the combined extract of *S.radiata*, and *H. poggeana* leaves on the lipid profile and kidney function indices of testosterone-induced benign prostatic hyperplasia in rats.

2. Materials and Methods

2.1. Chemicals and reagents

The chemicals and reagents used were obtained from Guangdong GuanghuaSci-Tech Company Ltd, India. Also, testosterone propionate and finasteride which served as BPH induction and curative agents were obtained from Laborate Pharmaceuticals Limited, India and Bafna Pharmaceuticals Limited, India, respectively, while assay kits from Randox Laboratories, United Kingdom, were employed in the laboratory analyses.

2.2. Collection and identification of plant materials

The leaves of *Spermacoce radiata* and *Hypselodelphyspoggeana* were obtained from a forestry garden belonging to the Department of Forestry, Michael Okpara University of Agriculture, Umudike (MOUAU), Abia State, Nigeria. The plants were identified and authenticated in the Department of Forestry, MOUAU, with avoucher specimen number: (*MOUAU/DF/BCH/03712*) and were kept in the herbarium unit of the Department for a referral. The plant materials were thoroughly cleaned, washed with tap water and air-dried at room temperature for 21 days to achieve a constant dry weight. The dried samples were pulverised into a coarse powder using an electric blender and stored properly for extraction.

2.3. Preparation of a combined plant extract

The combined ethanol extract of *S. radiata* and *H. poggeana* leaves (CESHL) used for the study was formulated by macerating 700 g of the combined plant sample containing 350 g of each of the ground plant leaves in a clean container with 1.8 L of absolute ethanol for 72 hours as earlier described by Uroko *et al.* (2020). It was then filtered with Whatman No one filter paper after 72 h and concentrated in a water bath at 45°C to remove the remaining ethanol from the combined extract. After which, the percentage yield of the combined extract was calculated and recorded.

2.4. Experimental animal

Fifty-one (51) male Wistar albino rats weighing 200 – 250 gwere obtained from the Department of Zoology and Environmental Sciences, University of Nigeria, Nsukka, Nigeria, and subjected to 2 weeks of acclimatisation in the animal house atthe Department of Biochemistry, College of Natural Science, MOUAU. The rats had free access to standard animal feed (Vital feed with 18% crude protein and 2800 kcal metabolisable energy) and clean drinking water following the guideline of the National Institute of Health for the care and use animals experiment (NRC, 2011). The experimental protocol was approved (MOUAU/VPP/EC/18/003) by the Ethics board of the

Department of Physiology, Biochemistry, and Pharmacology, Michael Okpara University of Agriculture, Umudike.

2.5. Acute toxicity (LD50) of the plants

The median lethal dose (LD_{50}) of the plant extract was determined by the method described by Lorke (1983) using21 rats. In the first phase, rats were divided into threegroups (3 rats per group) and were treated with the combined extract at doses of 10, 100, and 1000 mg/kg body weight orally. They were observed for 24 h for signs of toxicity.In the second phase, three rats each were treated with the same combined extract but at doses of 1600, 2900, and 5000 mg/kg body weight orally, respectively. A confirmatory test was conducted using three rats at 5000mg/kg. The median lethal dose (LD_{50}) was obtained using the second phase.

2.6. Induction of BPH

BPH was induced in the rats by subcutaneous injection of testosterone propionate mixed with olive oil at a ratio of 1:1 (v/v; 5 mg/kg body weight) for 28 consecutive days. The combined ethanol extract and finasteride respectively were administered orally 1 hour after the testosterone propionate (TP) injection for the 28 consecutive days.

2.7. Experimental design

A complete randomised experimental design comprising of five treatment groups (n = 6) was used for the study. Group 1 was the normal control that received no testosterone propionate injection but was administered 2 mg/kg olive oil/day for 28 days. Group 2 was the BPH control rats that received 5 mg/kg (BW) testosterone propionate/day without any treatment for 28 days. Group 3 was the standard control rats that received 5 mg/kg (BW) testosterone propionate/day and were treated with 5 mg/kg (BW) finasteride/day for 28 days. Group 4 was rats administered 5 mg/kg testosterone propionate/day and treated with 200 mg/kg (BW) CESHL/day for 28 days. While group 5 contains rats administered 5 mg/kg testosterone propionate/day and treated with 600 mg/kg (BW) CESHL/day for 28 days. The testosterone propionate was mixed with olive oil in ratio 2:1 (v/v) before its administration to the rats. The animals were weighed before the commencement of the experiment and subsequently every week till the end of the experiment.

2.8. Determination of biochemical parameters

After 28 days, the rats werefasted overnight and anaesthetised by brief exposure to trichloromethane vapour and bled by cardiac puncture. Blood samples were collected, and sera were carefully separated and used for the determination of various biochemical analyses. Each rat's carcass was promptly dissected, and the kidney tissues were collected for histological examination. Prostates were also carefully excised. Three prostates per group were randomly selected and freed of external fascias, washed in normal cold saline, blotted with filter paper and weighed on a sensitive balance to determine the prostate weight.

2.9. Determination of lipid profile

The high-density lipoprotein (HDL) concentration was determined according to the method of Allain *et al*. (1974), while the triacylglycerol (TAG) concentration serum total cholesterol and high-density lipoprotein (HDL) concentrations were determined using the method described by Albers *et al*. (1978). Also, the low-density lipoprotein (LDL) concentration was determined as described in the method of Friedelwald *et al.* (1972), whereas the method described by Albers *et al*. (1978) was used to determine the concentration of triacylglycerol (TAG).

2.10. Determination of serum urea and creatinine concentrations

The method of Fawcett and Scott (1960) was used to determinethe urea concentration with the Randox commercial kit. Likewise, creatinine concentration was determined using the method described by Henry (1974).

2.11. Histopathological examination

For the histopathological examination, the kidney sections were fixed in 10% phosphate-buffered formalin for a minimum of 48 hours before tissue preparation, after which they were prepared and examined as described by Uroko *et al*. (2020).

2.12. Statistical analysis

The data generated from the study were subjected to one analysis of variance (ANOVA) using a Statistical Products and Service Solutions (SPSS) version 22. The means were compared with Duncan's multiple range test, statistical significance was observed at 95 % confidence level ($P<0.05$), and results were presented

as mean ± standard deviation (n = 6). The results with different superscripts are significantly different (P<0.05) from any paired mean.

3. Results and discussion

The use of plants for medicinal purposes is increasingly becoming important in the treatment of numerous diseases. This is because plant medicines are relatively safe, more affordable and sometimes offers better therapeutic value than synthetic drugs.

3.1. Acute toxicity result

The acute toxicity test results of the combined ethanol extract of *S.radiata* and *H. poggeana* leaves on mice showed no death or any sign of toxicity in the rats at the highest dose of 5000 mg/kg except for the loss of appetite.

The combined ethanol extract of *S. radiata* and *H. poggeana* was not toxic to the animals because no death or any sign of toxicity was recorded even at a high dose of 5000 mg/kg. Thus, the lethal dose of 5000 mg/kg BW gotten in this study is suggestive of a high degree of safety of a combined extract of S. *radiata* and *H. poggeana*.

3.2. Effects of CESHL onbody weight and prostate weight of rats

The BPH-control group exhibited a decline in body weight by 20.9% and a significant (P<0.05) increase in prostate weight when compared with normal control (without BPH). The administration of extract orstandard drug (finasteride) improved thebody weight and significantly (P<0.05) reducedthe prostate weight of rats in treated groups close to normal, compared with the BPH control (untreated).

The BPH induction caused a significant reduction in the rate of gain of body weight and an increase in prostate weight in BPH control rats when compared with the normal control rats. However, the administration of extract andstandard drug (finasteride) respectively improved thebody weight and significantly reduced the prostate weight of rats in treated groups close to normal, compared with the BPH control (untreated). This is in agreement with the reports of Shin *et al*. (2012), who reported a reduction in body weight in the presence of BPH, which could be attributed to loss of appetite because of discomfort caused by induction of BPH. The body weight changes may serve as a sensitive indicator of the general health status of animals. The increase in prostate weight could be attributed to the growth in the number of cellular components of the prostate tissue (Akbari *et al.*, 2021). The result is in agreement with VeereshBabu *et al.* (2010), who reported an increase in prostate weight as one of the important biomarkers of BPH. As a result, many studies have tested the inhibitory effects of various substances on the development of BPH by measuring prostate weight.

Table 1. Effects of CESHL on body weight and prostate weight of BPH induced rats.

Groups	Body weight (g)	Prostate weight (g)
Normal control	231.20±4.22^{c}	0.42±0.07^{a}
BPH control	182.40±2.26^{a}	2.12±0.28^{c}
BPH+Finasteride	228.40±5.15^{c}	0.67±0.23^{a,b}
BPH+200mg/kg CESHL	214.60±6.24^{b}	0.81±0.36^{a,b}
BPH+600mg/kg CESHL	224. 80±8.30^{c}	0.73±0.34^{a,b}

Mean with different superscripts (a-b-c) are significantly different at (P<0.05) along with the columns.

3.3. Effects of CESHL on serum triacylglycerol (TAG) concentrations of BPH induced rats

There was a significant (P<0.05) increase in the serum triacylglycerol (TAG) concentrations of BPH induced rats (disease control) when compared with the normal control (Figure 1). Whereas the BPH rats treated with 5 mg/kg finasteride/d, 200 and 600 mg/kg CESHL/d respectively showed significant (P<0.05) reduction in the serum TAG concentrations when compared with the disease group. There were no significant (P>0.05) differencesin the serum TAG concentrations in the extract-treated groups in comparison with the normal control.

Serum TAG is one of the components of serum cholesterol regarded as bad lipids implicated in narrowing of arteries and atherosclerosis due to their deposition on the arterial walls, which increases blood pressure and risks of cardiovascular disorders, inflammation of vital organs like kidneys and paralysis of body parts. The significantly elevated serum TAG level in the BPH control relative to the normal control showed that dyslipidemia might be implicated in the pathogenesis of BPH, which aligns with the reports by Parsons *et al*. (2008) that hyperlipidemia worsens BPH progression. However, the significant decline in the serum TAG levels of the BPH induced rats treated with finasteride and various doses of CESHL in comparison

with the BPH control, respectively, could be attributed to anti-BPH and anti-dyslipidemic effects of CESHL. These showed that maintaining a healthy lipid profile playsa critical role in managing BPH progression, which agrees with the findings of Lekili*et al.* (2006) that reducing the serum levels of LDL and TAG retards BPH progression and prevents complications commonly associated with aggressive BPH.

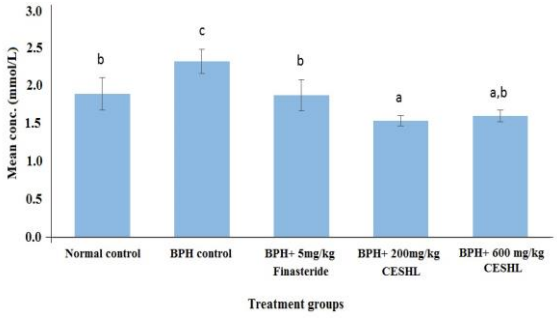

Fig. 1. Triacylglycerol (TAG) concentrations of BPH induced rats treated with CESHL. Bars with different superscripts are significantly different (p<0.05) from any paired mean.

3.4. Effects of CESHL on serumhigh-density lipoprotein (HDL) concentrations of BPH rats

The results in Figure 2 indicated a significant (P<0.05) reduction in the serum high-density lipoprotein (HDL)concentration of the BPH control. All the BPH induced rats treated with standard drug (5mg/kg), 200 and 600 mg/kg CESHL/d indicated a significant (P<0.05) increase in the serum HDL concentration in comparison with the BPH control, respectively. However, the difference was not significant (P<0.05) when compared with the normal control.

High-density lipoprotein (HDL) is a healthy part of cholesterol that transport unhealthy cholesterol, including LDL and TAG,from the arterial walls to the liver, thereby preventing high blood pressures, atherosclerosis, stroke and cardiovascular diseases (Dahle *et al.*, 2002). The significantly reduced HDL concentrations in the BPH control, when compared with the normal control, suggests dyslipidemia which predisposed the rats to adverse health effects of abnormal lipid profile including atherosclerosis and heart diseases due to inefficient transport and metabolism of LDL and TAG in the liver (AUA Practice Guidelines Committee (2003). However, the marked elevation of HDL concentrations in the BPH induced rats treated with finasteride and various doses of CESHL, respectively, showed that each of the treatments was able to restore the altered HDL concentration to normal concentrations in the rats. The high HDL concentrations in the CESHL treated BPH induced rats would ensure efficient transport of LDL and TAG from the arterial walls and their utilisation in the liver, thereby averting health consequences associated with the excess accumulation of LDL and TAG in the blood and their subsequent deposition on the blood vessels (AUA Practice Guidelines Committee (2003). Therefore, maintaining high HDL concentration and low LDL in BPH patients may improve treatment outcomes.

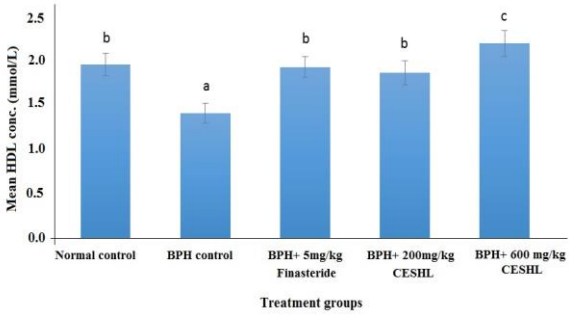

Fig. 2. High-density lipoprotein (HDL) levels of BPH induced rats treated with CESHL. Bars with different superscripts are significantly different (p<0.05) from any paired mean.

3.5. Effects of CESHL on serum cholesterol (CHOL) concentrations of BPH induced rats

The data in Figure 3 indicated a significant (P<0.05) increase in the serum cholesterol (CHOL) concentration in BPH control rats. A significant (P<0.05) reduction in the serum CHOL concentration of BPH induced rats treated with 200 and 600 mg/kg CESHL/d was recorded when compared with the BPH and normal control, respectively. However, there was no significant (P>0.05) increase in the serum CHOL concentration of the BPH induced rats treated with 5 mg/kg finasteride/d in comparison with the normal control.

The increased serum cholesterol levels in BPH control and BPH induced rats treated with finasteride showed that BPH causes abnormal lipid profile that could increase the risk of atherosclerosis and worsen BPH progression and survival chance of the patients if not given the right treatment, which agrees with the

earlier findings by Lekili *et al*. (2006). The increased cholesterol level in the finasteride-treated BPH induced rats suggest that finasteride does not possess adequate anti-cholesterolemia effects and should be administered with a cholesterol-lowering drug to achieve maximum therapeutic effects. On the other hand, the very low serum cholesterol level observed in the BPH induced rats treated with CESHL suggest that CESHL is a good cholesterol-lowering agent that may be critical in preventing atherosclerosis and other complication associated with untreated BPH.

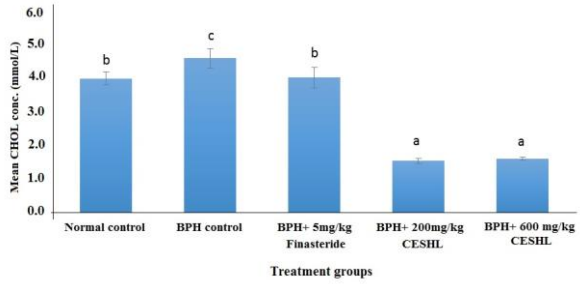

Fig. 3. Cholesterol (CHOL) concentrations of BPH induced rats treated with CESHL. Bars with different superscripts are significantly different (P<0.05) from any paired mean.

3.6. Effects of CESHL on serum low-density lipoprotein (LDL) concentrations of BPH induced rats

The serum low-density lipoprotein (LDL) concentration of the BPH control group increased significantly (P<0.05) when compared with the serum LDL concentration of the normal control. However, there wasa significant (P<0.05) reduction in the serum LDL concentrations of BPH induced rats treated with 5 mg/kg finasteride/d, 200 and 600 mg/kg CESHL/d when compared with the BPH controlgroup, respectively. Besides, the LDL concentrations of the BPH induced rats treated with 200 and 600 mg/kg CESHL/d showed no significant (P>0.05) reduction when compared with the normal control.

The increased serum LDL concentration in the BPH control rats show that BPH, when left untreated, is associated with elevated LDL level and adverse health effects dyslipidemia. The BPH control rats were likely to suffer narrowing of blood vessels, high blood pressure and increased risk of cardiovascular disorders that could reduce their survival chance unless it was reversed on time. Treatments of the BPH induced rats with finasteride and various doses of CESHL respectively reduced the serum LDL concentrations in the rats significantly, indicating that CESHL possesses high LDL loweringactivity which, prevent accumulation of LDL and its associated adverse health consequences and aligns with findings of Lekili *et al*. (2006).

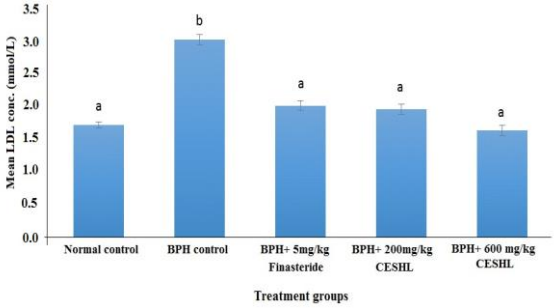

Fig. 4. Low-density lipoprotein (LDL) of BPH induced rats treated with CESHL. Bars with different superscripts are significantly different (p<0.05) from any paired mean.

3.7. Effects of CESHL on the serum urea concentrations of BPH induced rats

The results in Figure 5 showed a significant (P<0.05) increase in the serum concentrations of the BPH control and BPH induced rats treated 5 mg/kg finasteride/d. Treatments of BPH induced rats with 5 mg/kg CESHL/d, 200 and 600 mg/kg CESHL/d respectively showed significant (P<0.05) reduction in the serum urea concentrations when compared with the BPH control.But the difference seen in the same groups was not significant (P>0.05) when compared with the normal control.

Toxic effects of any substance on the kidney are represented through the structural damage and changes in the excretory function of the kidney. In this study, urea and increased significantly (P<0.05) in BPH control, suggesting a decline in glomeruli filtration rate when compared to BPH induced rats treated with finasteride and graded doses of CESHL, respectively. This finding agrees with the earlier findings by Weinstein *et al*. (2009) that BPH causes significant elevation of the serum urea concentration. The elevation in urea concentration caused by BPH was significantly (P<0.05) lowered by the standard drug, 200 and 600 mg/kg of the combined extract. Changes in urea and creatinine levels indicate that the BPH condition may pose serious damaging effects on the kidney eventually. Urea is a key metabolic product of biological pathways comprising ammonia, which is harmful to the body (Zhang *et al.*, 2008). Therefore, its

transportation plays a vital part in nitrogen removal and osmotic homeostasis. This is in agreement with the report of Asuk and Ugwu (2018), who reported a reduction in urea and creatinine levels in BPH-induced rats treated with *Vernoniaamygdalina*.

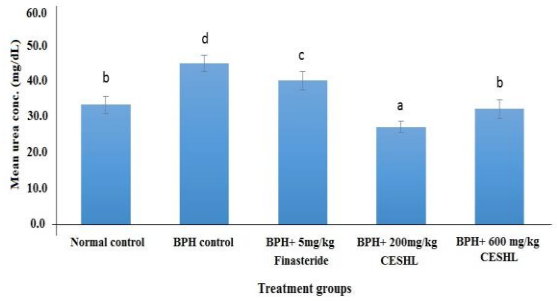

Fig. 5. Urea concentrations of BPH induced rats treated with CESHL. Bars with different superscripts are significantly different (P<0.05) from any paired mean.

3.8. Effects of CESHL on the serum creatinine concentrations of BPH induced rats

The data in Figure 6 indicated a significant (P<0.05) increase in the serum creatinine concentration in the BPH control group when compared with the normal control. However, a significant (P<0.05) reduction in the serum creatinine concentration was seen in BPH induced rats treated with 5 mg/kg drug, 200 and 600mg/kg CESHL/day comparable to the BPH control but were not significant (P>0.05) when compared with the normal control.

Creatinine in serum is connected with a great risk of prostate cancer, especially in progressive cases where the risks of survival are low Weinstein *et al*. (2009) and are also regarded as a veritable prostate cancer staging and predictive marker (Chiong *et al*., 2005). Therats in the BPH control group showed an elevated level of creatinine when compared to the normal control, signifying impaired kidney function. However, treatment with the combined extract caused a significant (P<0.05) reduction in creatinine concentration when compared to the BPH-induced group. This result agrees with that of Reshma *et al*. (2014), who evaluated markers of renal dysfunction in prostate disorders with normal controls. The ability of the combined extracts to reverse the alterations in the excretory function of the kidney, which was impaired by the prostate disorder, shows that the combined extract seems to be effective in ameliorating renal impairment in BPH disorder. This could be attributable to the presence of various complex phytochemical compounds in the plants.

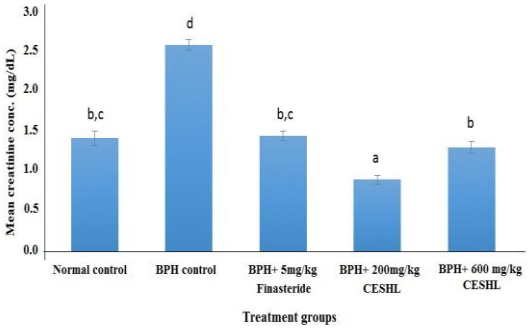

Fig. 6. Creatinine concentrations of BPH induced rats treated with CESHL. Bars with different superscripts are significantly different (P<0.05) from any paired mean.

3.9. Photomicrographs of kidney sections of BPH induced rats treated with CESHL

The sections of the kidneys in the photomicrographs in Figure 7–12 indicated normal renal histomorphology for laboratory rodents with normal glomeruli (G) in the cortex, surrounded by normal renal tubules (Arrow). The renal tubules were also normal in the outer medulla and the inner medulla, Renal artery (RA), and Renal vein (RV).

The histology of kidney sections in all groups indicated no significant alterations in the renal structures despite the impairment in renal function. This shows that the combined extract of *S. radiata* and *H. pogeana* leaves had no negative impact on the kidney tissue histo-architecture despite the observed decline in renal functions. However, the extract possesses the potential of ameliorating cardiovascular diseases and atherosclerosis by regulating the lipid profile and protecting against kidney damage in BPH.

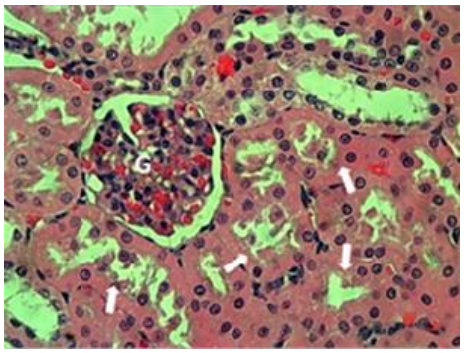

Fig. 7. Histomorphology of kidney section from normal control rats showing evenly distributed open glomerular capillaries and normal interstitial haemorrhage.

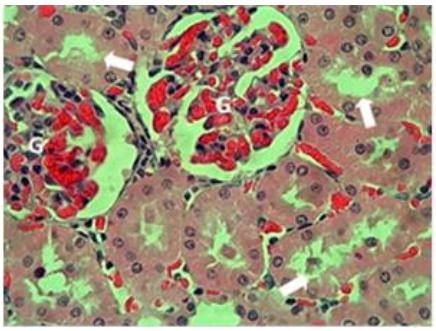

Fig. 8. Histomorphology of kidney section from BPH control showing inflammatory cells and proliferating mesangial cells.

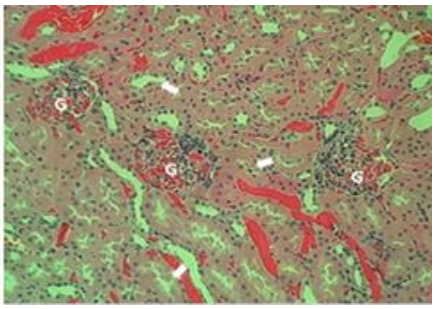

Fig. 9. Histomorphology of kidney section from benign prostatic hyperplasia induced rats treated with 5 mg/kg of finastride (standard drug) showing regenerated normal cells.

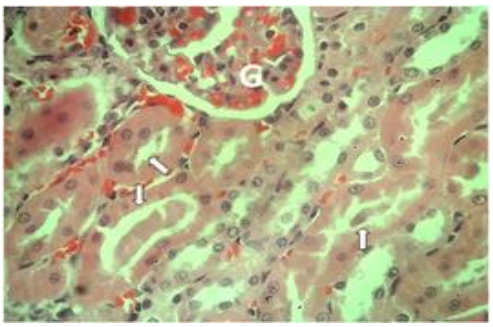

Fig. 10. Histomorphology of kidney section from benign prostatic hyperplasia induced rats treated with 200 mg/kg CESHL/d showing moderate endotheliu and interstitial haemorrhage.

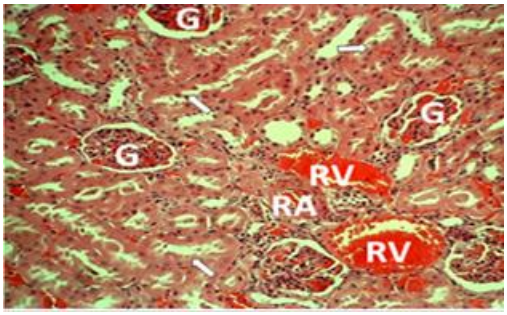

Fig. 11. Histomorphology of kidney section from benign prostatic hyperplasia induced rats treated with 600 mg/kg CESHL/d showing evenly distributed normal endotheliu and interstitial haemorrhage.

4. Conclusion

The findings from this study show that the combined extract of *S. radiata* and *H. poggeana* has the potential of averting the risks of hyperlipidaemia by regulating the metabolism of lipid and protecting against renal damagein treated rats, hence, indicating a neuroprotective property that seems to be significant in the management of benign prostate hyperplasia. Further studies are pertinent to identify the exact constituents of the plant extracts responsible for these observed effects.

5. Acknowledgements

The authors wish to thank the technical staff in the Laboratory Unit of the Department of Biochemistry for their assistance throughout this study.

6. References

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