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Research Article
Sphenostylis stenocarpa Seed Extract Attenuates Dyslipidemia in Testosterone Propionate-induced Benign Prostatic Hyperplasia in Rats

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Abstract

Background and Objective: Benign Prostatic Hyperplasia (BPH) is a prevalent disease among older men caused by abnormal proliferation of the prostatic cells. Findings indicate an association between dyslipidemia and BPH. This study aimed at evaluating the effect of ethanol extract of *Sphenostylis stenocarpa* seed on the lipid profile of rats with testosterone propionate-induced BPH. **Materials and Methods:** A total of 25 male Wistar rats randomized into five groups of five rats each were used. BPH was induced in the rats by subcutaneous injection of testosterone propionate in olive oil for 28 days. The test rats (after BPH induction) were treated with ethanol extract of the plant seed at doses of 200 and 400 mg kg^{-1} b.wt. The concentrations of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triacylglycerol were evaluated on the sera of the rats. **Results:** The BPH control rats (model group) showed a significant ($p<0.05$) increase in concentrations of total cholesterol, LDL-C, triacylglycerol, with a significant decrease in HDL-C compared to the normal control. Oral administration of the seed extract to the rats significantly reversed these dyslipidemia indicators when compared to the model group. **Conclusion:** This study has shown that ethanol extract of *S. stenocarpa* seed ameliorated dyslipidemia in testosterone propionate-induced BPH in rats. This suggests that the plant seed may be useful in the prevention of cardiovascular disease.

Key words: BPH, testosterone propionate, dyslipidemia, cardiovascular diseases, *Sphenostylis stenocarpa*, seed extract, rat model

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Benign Prostatic Hyperplasia (BPH) is a prevalent disease among older men, caused by abnormal proliferation of the prostatic cells. BPH comes next to coronary heart disease, hypertension and diabetes among diseases that affect elderly men above 50 years[1]. The enlarged prostate affects the quality of life of the sufferer, predisposing them to acute and chronic urinary retention, urinary tract infection, bladder damage and renal failure[2]. The BPH etiology has not been well elucidated, though ample evidence has linked androgens to prostate differentiation and growth[3].

Furthermore, research findings have reported that metabolic syndrome (MetS) or its components may be linked with BPH[4,5], although the underlining mechanism is still poorly understood. MetS is a cluster of clinical diseases including hypertension, obesity, dyslipidemia, insulin resistance and impaired glucose metabolism which increases the risk of diabetes type 2 and cardiovascular disease[4,6]. Dyslipidemia is characterized by an elevated level of total cholesterol, Low-Density Lipoprotein Cholesterol (LDL-C), triacylglycerol and significantly reduced High-Density Lipoprotein Cholesterol (HDL-C). Hardik *et al*.[7] and Nandeesha *et al*.[8] have reported an association between BPH and dyslipidemia, the latter frequently occurs in association with cardiovascular complications[9]. Cardiovascular Diseases (CVD) are presently the leading cause of death worldwide and their etiologies are partly associated with oxidative stress[10], a factor that promotes BPH as well. Oxidative stress comes with a weakened endogenous antioxidant defense system which may cause cellular damage and worsen cardiovascular diseases[10].

In recent years, much attention has been drawn to the use of phytotherapy in combating diseases. The cardioprotective effect of food plants has been linked to the inherent nutrient which includes antioxidant vitamins, minerals, phytochemicals and plant protein[11]. Scientific research has shown that *Sphenostylis stenocarpa* seed contains 66% unsaturated fatty acids[12], which are known to exhibit cardiovascular protective effect[11]. Enujiugha *et al*.[13] reported the radical scavenging capacity of the plant seed due to its high phenolic content. Ajibola *et al*.[14] reported the usefulness of *Sphenostylis stenocarpa* protein hydrolysate as antioxidants in the management of oxidative stress-related metabolic disorders. The anti-fibrotic and hepatoprotective potentials of the plant seed against carbon tetrachloride-induced liver injury in male Wistar rats via antioxidant and anti-inflammation properties have also been stated[15]. Therefore, the study is aimed at evaluating the effect of S*phenostylis stenocarpa* seed extract on the lipid profile of the BPH rats.

MATERIALS AND METHODS

Study area: The laboratory work was conducted at the laboratory of Chemistry/Biochemistry Department, Alex Ekwueme Federal University Ndufu-Alike, Nigeria as well as Department of Medical Biochemistry of the same Institution from October, 2018-February, 2019.

Chemicals: Testosterone Propionate (TP) was purchased from Sigma-Aldrich chemical company, Germany. Finstals-5® (Finasteride) was the product of Stallion Laboratories PVT. Limited, Gujarat, India. Reagents used for the lipid profile were commercial test kits and products of Quimica Clinica Aplicada (QCA), Spain and Randox Laboratories Ltd., Crumlin, Antrim, UK. All other chemicals and reagents used for the study were of analytical grade.

Preparation of the seed extract: Dried seeds of *S. stenocarpa* were bought from the Ogbete main market in Enugu, Enugu State, Nigeria. The seeds were carefully selected, washed, dried and ground coarsely with a laboratory mill. The coarse sample was extracted with ethanol solvent using a soxhlet extractor. A rotary evaporator (Heidolph, USA) was used to separate the extract from the solvent and the extract stored in the refrigerator at a temperature of 4°C.

Acute toxicity study: The method of Lorke[16] was used for the evaluation of the median Lethal Dose (LD_{50}) of *S. stenocarpa* seed extract. Thirteen albino mice weighing 20-25 g were acclimatized to the animal house for 7 days. They were subsequently assigned to diverse groups for the lethal dose test which was carried out in two stages. In the first stage, the animals were randomized into three different groups of three mice each and were administered graded oral doses of 10, 100 and 1000 mg kg^{-1} b.wt., respectively of the seed extract. In the second stage, three mice placed in three different groups were orally administered 1600, 2900 and 5000 mg kg^{-1} b.wt., of the extract while one mouse served as control. The mice were monitored for 24 hrs for toxicity signs and possible death. The LD_{50} of the seed extract was above 5000 mg kg^{-1} hence the doses of 200 and 400 mg kg^{-1} b.wt., were chosen for the study. The mice were handled according to the Guideline for the Care and Use of Laboratory Animals[17].

Experimental design: Twenty-five male Wistar rats weighing 180±0.5 g were used for this study. They were procured from TwinVet Resource farm, nearby the University of Nigeria, Nsukka. The rats were acclimatized to the animal house for 7 days and were allowed unrestricted access to standard

Table 1: Study groups and treatment design

Groups	Subcutaneous injection	Oral administration
Normal control	Olive oil 1 mL kg^{-1}	Physiological saline 2 mL kg^{-1}
Model group	TP (3 mg kg^{-1})	Physiological saline 2 mL kg^{-1}
Positive control	TP (3 mg kg^{-1})	Finasteride (5 mg/70 kg)
TP+SsEE (200 mg kg^{-1})	TP (3 mg kg^{-1})	SsEE (200 mg kg^{-1})
TP+SsEE (400 mg kg^{-1})	TP (3 mg kg^{-1})	SsEE (400 mg kg^{-1})

TP: Testosterone propionate, SsEE: *Sphenostylis stenocarpa* ethanol extract

pellet food (Vital Feeds Nigeria Ltd, Jos, Nigeria) and clean water *ad libitum*. The ethics approval of the study was obtained from the Ethics and Biosafety Committee, Faculty of Biological Sciences, University of Nigeria, Nsukka (UNN/FBS/EC/1010).

The acclimatized rats were randomly divided into 5 groups (n = 5) and the treatment design was as represented in Table 1.

The induction of BPH to the experimental rats was achieved by subcutaneous injection of testosterone propionate (3 mg kg^{-1} b.wt., dissolved in olive oil) for 28 days[18]. The experimental rats (after BPH induction) were treated with ethanol extract at doses of 200 and 400 mg kg^{-1} b.wt., for 7 days. On day 36th, fasted rats were sacrificed and sera obtained from blood samples were used for some biochemical analysis.

Biochemical analysis: Estimation of serum total cholesterol concentration was carried out according to the method of Allain *et al.*[19], serum HDL-C and triacylglycerol concentrations were determined following the method of Albers *et al.*[20] and concentration of LDL-C was calculated by the method of Friedwald *et al.*[21]. Fasting blood glucose concentration was measured with the Accu-Check Glucometer.

Statistical analysis: The Statistical Package for the Social Sciences (SPSS) software version 20.0 (IBM Corp., Atlanta GA) was used for data analysis. Results were expressed as Mean±Standard Error of the Mean (SEM) and tests of statistical significance were estimated using one-way analysis of variance followed by post hoc multiple comparisons, with the Duncan test to detect significant differences between the groups at $p<0.05$.

RESULTS

Effect of *Sphenostylis stenocarpa* ethanol extract on total cholesterol concentration of the BPH rats: The subcutaneous injection of TP caused a significant increase ($p<0.05$) in the concentration of total cholesterol from 4.03±0.05-4.93±0.40 mmol L^{-1}. However, oral administration of the seed extract to the BPH rats clearly reversed the effect of the exogenous hormone on the total cholesterol concentration, the values obtained (4.10±0.12, 4.20±0.12 mmol L^{-1} for rats administered 200 and 400 mg kg^{-1} extract respectively) were not significantly different from normal control (Fig. 1).

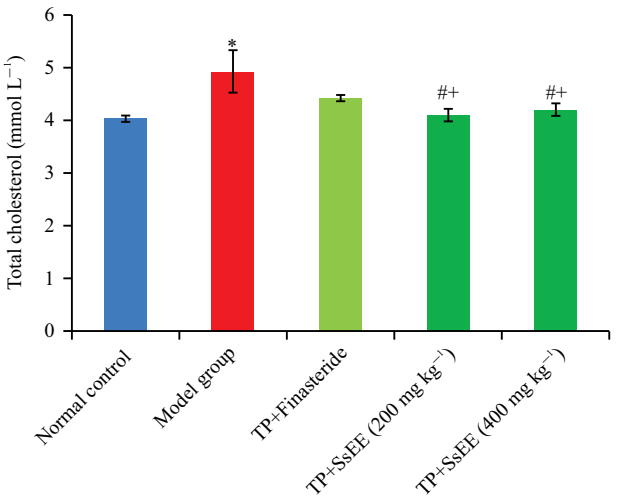

Fig. 1: Effect of *Sphenostylis stenocarpa* Ethanol Extract (SsEE) on total cholesterol concentration in Testosterone Propionate (TP)-induced BPH rats

Values are expressed as Mean±SEM (n = 5). *Significant when compared to normal control ($p<0.05$), #Significant when compared to model group, +Significant when compared to TP+finasteride group ($p<0.05$)

Effect of *Sphenostylis stenocarpa* ethanol extract on triacylglycerol concentration of the BPH Rats: The triacylglycerol concentration of the model group with experimentally induced BPH (1.37±0.10 mmol L^{-1}) was shown to be significantly higher compared to the concentration of the normal control (1.18±0.01 mmol L^{-1}). Treatment of the rats with the seed extract significantly reduced the triacylglycerol concentration to near normal (1.17±0.01, 1.15±0.01 mmol L^{-1} for rats that received 200 and 400 mg kg^{-1} extract, respectively) (Fig. 2).

Effect of *Sphenostylis stenocarpa* ethanol extract on LDL-C concentration of the BPH rats: There was a significant

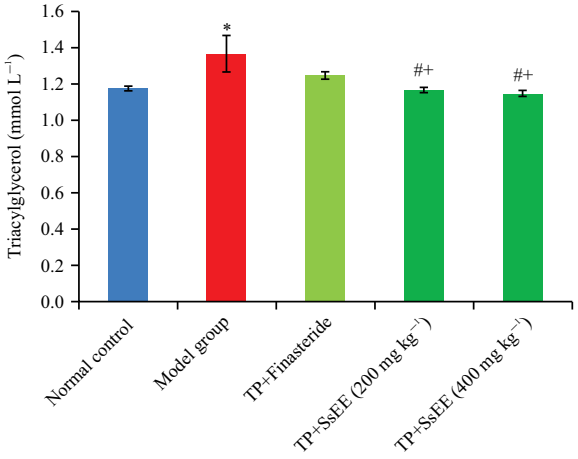

Fig. 2: Effect of *Sphenostylis stenocarpa* Ethanol Extract (SsEE) on triacylglycerol concentration in Testosterone Propionate (TP)-induced BPH rats

Values are expressed as Mean±SEM (n = 5). *Significant when compared to normal control (p<0.05), #Significant when compared to the model group, +Significant when compared to TP+finasteride group (p<0.05)

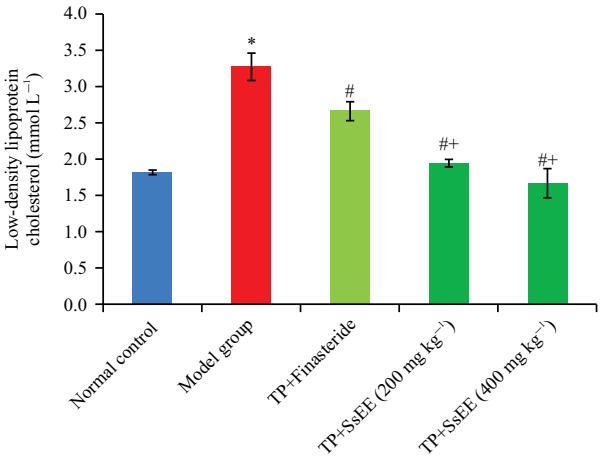

Fig. 3: Effect of *Sphenostylis stenocarpa* ethanol extract (SsEE) on the concentration of low-density lipoprotein cholesterol in Testosterone Propionate (TP)-induced BPH rats

Values are expressed as Mean±SEM (n = 5). *Significant when compared to normal control (p<0.05), #Significant when compared to the model group, +Significant when compared to TP+finasteride group (p<0.05)

increase in LDL-C concentration of rats in the model group (3.28±0.19 mmol L^{-1}) when compared to the normal control group (1.82±0.02 mmol L^{-1}). Treating the BPH rats with the ethanol extract significantly reduced the LDL-C concentration to 1.67±0.20 mmol L^{-1} for rats that received the highest dose,

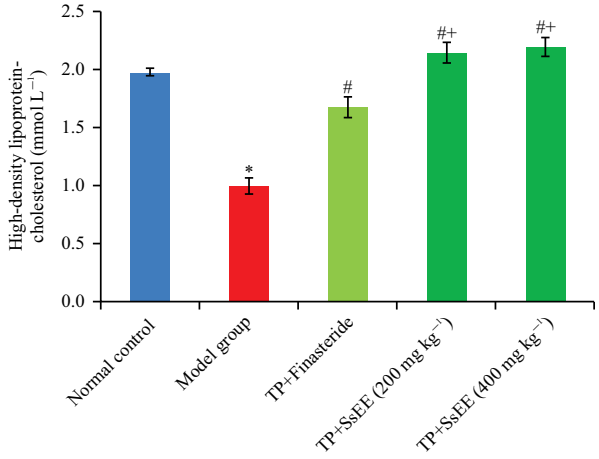

Fig. 4: Effect of *Sphenostylis stenocarpa* Ethanol Extract (SsEE) on the concentration of high-density lipoprotein cholesterol in Testosterone Propionate (TP)-induced BPH rats

Values are expressed as Mean±SEM (n = 5). *Significant when compared to normal control (p<0.05), #Significant when compared to model group, +Significant when compared to TP+finasteride group (p<0.05)

when compared to the model group that received the hormone alone (Fig. 3) and the values where not significantly different from the normal control. Furthermore, it was shown that *S. stenocarpa* seed extract significantly reduced LDL-C concentration compared to the standard drug (finasteride).

Effect of *Sphenostylis stenocarpa* ethanol extract on HDL-C concentration of the BPH rats: The concentration of serum HDL-C significantly reduced in the group that received the hormone alone (1.00±0.07 mmol L^{-1}) when compared to the normal control group (1.98±0.03 mmol L^{-1}). However, the administration of the seed extracts significantly ($p<0.05$) increased the concentration of HDL-C of the test groups (2.15±0.09, 2.2±0.08 mmol L^{-1} for rats administered 200 and 400 mg kg^{-1} dose, respectively) when compared to the model and positive control groups (Fig. 4).

Effect of *Sphenostylis stenocarpa* ethanol extract on blood glucose concentration of the BPH rats: There was a significant ($p<0.05$) increase in the fasting blood glucose concentration of the rats that received only the hormone (70.00±4.30 mg dL^{-1}) when compared to the rats in normal control (56.75±2.84 mg dL^{-1}). Treatment of the rats with *Sphenostylis stenocarpa* extract significantly reduced the fasting blood glucose concentration to 53.25±2.50 mg dL^{-1} for the rats that received 400 mg kg^{-1} dose, when compared

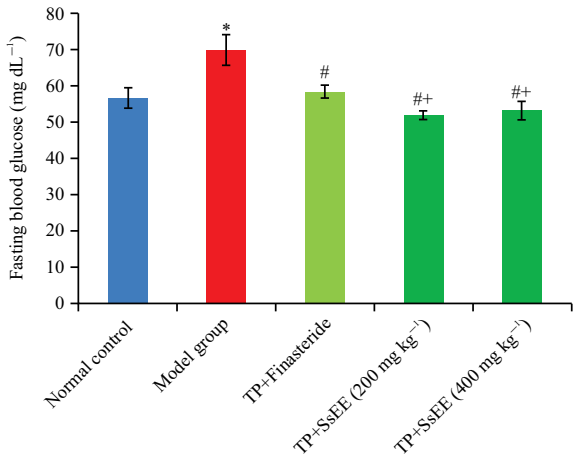

Fig. 5: Effect of *Sphenostylis stenocarpa* Ethanol Extract (SsEE) on fasting blood glucose concentration in Testosterone Propionate (TP)-induced BPH rats

Values are expressed as Mean±SEM (n = 5). *Significant when compared to normal control ($p<0.05$), #Significant when compared to model group, +Significant when compared to TP+finasteride group ($p<0.05$)

to the group that received only the hormone. The values obtained after treatment with the extract were not significantly different ($p>0.05$) from the normal and positive control groups (Fig. 5).

DISCUSSION

From our results, we found coexistence between BPH and dyslipidemia (a component of MetS), rats in the model group (BPH induced rats without treatment) showed an elevated concentration of total cholesterol, LDL-C and triacylglycerol with a corresponding reduced concentration of HDL-C. This indicated that BPH development and dyslipidemia may have a common pathogenic mechanism. This finding is not deviant from previous studies where a positive association was established between BPH and MetS[22,23], suggesting that BPH may predispose its sufferers to cardiovascular complications. Dyslipidemia in particular has been reported to trigger cardiovascular events[9].

Cardiovascular diseases are one of the leading causes of disability and death globally[24]. Scientific reports have established a direct relationship between serum LDL-C and CVD complications[25,26]. A reduced concentration of HDL-C and elevated LDL-C as observed in this study are factors associated with stroke and myocardial infarction[27]. The result is explainable as dyslipidemia which is depicted in rats in the model group is believed to promote atherosclerosis and a major menace for adverse cardiovascular complications[9]. The management of dyslipidemia is focused mainly on the reduction of serum LDL-C concentration[28] and various reports have shown that plant derived foods can proffer such a protective role against this menace[29,30]. The cardioprotective effect of plant derived food is due to inherent beneficial nutrients in them such as unsaturated fatty acids, antioxidant vitamins, minerals, phytochemicals and plant protein[11].

From the results, *Sphenostylis stenocarpa* seed extract significantly lowered the concentrations of total cholesterol, triacylglycerol and low-density lipoprotein cholesterol and increased the concentration of high-density lipoprotein cholesterol when compared to the model group. This is a clear indication of a possible protective role of the plant seed in cardiovascular complications. This beneficial effect is attributed to the established nutritional composition of the plant seed such as potent antioxidant capacity[13-15], unique amino acid profile[14], and fatty acids constituents comprising 66% unsaturated fatty acids[12,31], which are known to exhibit cardiovascular protective effects[11].

The result of the blood glucose concentration of this study also suggests a possible protective role of the plant seed. An unusually elevated blood glucose concentration is a glycemic disorder that progresses to diabetes mellitus[32] which correlates positively with BPH[33] and cardiovascular diseases[34]. The elevated fasting blood glucose concentration as observed in the BPH rats indicated some form of complications. This is because an impaired blood glucose metabolism and dyslipidemia have been reported to cause multiple organ damage leading to coronary heart disease and stroke[34]. The protective effect of the seed extract against cardiovascular diseases is further strengthened by the decreased concentration of fasting blood glucose concentration as observed in the rats treated with the plant extract.

CONCLUSION

In conclusion, the results of this study showed that the ethanol extract of *Sphenostylis stenocarpa* seeds attenuated dyslipidemia in BPH rats. The plant seed may be useful in the prevention of possible cardiovascular disease associated with BPH. Further studies are therefore recommended to elucidate other mechanisms of action of the plant seed.

SIGNIFICANCE STATEMENT

This study discovered that ethanol extract of *Sphenostylis stenocarpa* seeds could reverse the alterations in total cholesterol, triacylglycerol, LDL-C, and HDL-C in rats with induced BPH, which can be beneficial for the prevention of

possible cardiovascular disease associated with BPH. This study may facilitate the development of healthy food supplements from this underutilized traditional food crop that will play important role in the management of dyslipidemia and its associated complications.

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