

1 **Effect of *Ocimum gratissimum* leaf Extract on Lipid**

2 **Profile of Experimentally Induced Prostatic Hyperplasia**

3 **Animal Model**

4 **Abstract**

6 **Background:** Benign Prostate hyperplasia (BPH) is a highly prevalent disease among older
 7 men and a substantial public health problem. We investigated leaf extract of *Ocimum*
 8 *gratissimum* (OG) effect on lipid prolife in BPH.

9 **Methods:** BPH was induced in male rats weighing 200-300g through exogenous
 10 administration of testosterone and estradiol. Thirty (30) rats were divided into five groups.
 11 Four groups received subcutaneous injections of the two hormones and one group was used
 12 as a control with injections of hormones. Groups I to II were administered orally with
 13 different doses of extract and group III received standard drug, group IV was not treated and
 14 group V served as normal control. After Thirty-five days of treatment, the rats were sacrificed
 15 and blood collected through cardiac puncture for biochemical analysis. The prostate were
 16 harvested and weighed.

17 **Results:** In rats treated with extract and standard drug a significant decrease in the size of the
 18 enlarged prostate was observed ($p<0.05$) when compared with the BPH control group.
 19 Weight gain was observed in rats treated with extract and finasteride. The level of
 20 cholesterol, LDL-C and VLDL-C were significantly reduced while HDL-C increased when
 21 compared to the BPH control.

22 **Conclusion:** The significant reduction of cholesterol, LDL, VLDL-C and increase in HDL-C
 23 in the treated groups supported by decline in prostate weight suggest that the extract have the
 24 capacity of managing the lipid alterations caused by induction of BPH in rats.

25 **Keywords:** Testosterone, estradiol, Lipoprotein, Prostate, *Ocimum gratissimum*

26 **1. Introduction**

27 Benign Prostate hyperplasia (BPH) is a common disease in the aging men and causes
 28 substantial adverse health effects. BPH, leading to enlargement of the prostate and in turn
 29 resulting in lower urinary tract symptoms (LUTS), has high prevalence and socio-economic
 30 burden [1, 2, 3]. Therefore, it is important to determine the risk factors of BPH progression
 31 and to keep men away from them. However limited data are available concerning factors that
 32 might be protective against the development of BPH. Recently a growing amount of research-
 33 es demonstrated that metabolic syndrome (MS) and/or its individual components are involved
 34 in the development and progression of BPH [4, 5, 6]. The individual components of MS,
 35 including insulin resistance [7], dyslipidemia [8], obesity [9], hypertension [10] and the
 36 syndrome itself might predispose patients to greater risks of BPH and LUTS.

37 Available data indicate that BPH patients have higher total cholesterol (TC) and low-
 38 density lipoprotein cholesterol (LDL-C) levels and lower high-density lipoprotein cholesterol
 39 (HDL-C) levels compared with non-BPH patients [11]. Furthermore several reports sug-
 40 gested that BPH is one of components of MS [12]. With the accumulation of knowledge
 41 about MS and BPH, it has been known that insulin resistance (IR) is the cornerstone of MS
 42 and play a critical role in the growth of prostate and the progression of BPH [13, 14]. In
 43 additional to IR, inflammation and oxidative stress were reported to involve in the
 44 development and progression of BPH [15, 16, 17]. Despite the fact that the association
 45 between prostate diseases and MS is generally accepted, the pathogenetic link still needs to
 46 be deeply elucidated.

47 Scientific evaluation of medicinal plants is important to the discovery of novel drugs
 48 and also helps to assess toxicity risks associated with the use of either herbal preparations or
 49 conventional drugs of plant origin. *Ocimum gratissimum* contain different compounds such as

alkaloids, saponins, tannins, anthraquinone, flavonoids, steroids, terpenoids and cardiac glycosides [18, 19, 20] which makes it useful in traditional medication. This study investigated the usefulness of the leaf extract of *Ocimum gratissimum* in the management of the experimentally hormone-induced BPH in Wistar rats and its effect on lipid metabolism. The results will contribute to the search for locally available phytotherapeutic agents that can help in managing this debilitating disease especially in among the poor ones.

2. Materials and Methods

2.1. Plant Material

Fresh leaves of *Ocimum gratissimum* was harvested from a garden in Okuku in Yala Local Government of Cross River State, South-South, Nigeria. The plant was identified at the herbarium unit of the Department of Biological Sciences, University of Calabar. Their fresh leaves were washed and dried under the shade for seven days. The dried leaves were pulverized using pestle and mortar to get a powder that was used for extraction.

2.1.1. Preparation of extract

The powdered sample of *Ocimum gratissimum* 200g was soaked into 200ml of distilled water, this was filtered after 48 hours and filtrate was concentrated in water bath. The solutions were diluted with corn oil, to produce a solution 100mg/ml. The administration of extract was totally by gavage.

3.0 Hormones

Testosterone propionate Brand name: Ricostrone; a product of Greenfield pharma, Jiangsu Co Ltd., China. Estradiol valerate (by Medipharma Ltd., 108-Kotlakhpat industrial Est; Lahore, India. Testosterone propionate (T) and estradiol valerate E₂ (puregynon depot) were used for the induction of prostate enlargement at a dose of 400µg T and 80µg E₂ [21].

73 This was administered to the rats for three weeks subcutaneously in the inguinal region. All
74 Chemicals used in this study were of analytical grade and were obtained from reputable
75 companies.

76 **3.1. Animals**

77 A total of thirty (30) Wistar rats weighing between 200-300g were obtained from the
78 animal house of the Faculty of Basic Medical Sciences, Cross River University of
79 Technology, Okuku Campus, Nigeria. The rats were used for the experiment. The rats were
80 acclimatized for two weeks before the experiment commences. The rats were exposed to
81 approximately 12-hour light/dark cycles under humid tropical conditions, given tap water and
82 feed *ad libitum*, and were housed in standard plastic cages (five per cage) throughout the 35-
83 day duration of the study. The animal room was well be ventilated with a temperature range
84 of 27-29 °C. The Institutional Animal Ethics Committee approved the study before the
85 experiment and certified all experimental protocols.

86 **2.3.1. Induction of BPH**

87 BPH was induced by exogenous administration of testosterone and estradiol in
88 staggered doses (three times a week respectively) for three weeks according to [21] with
89 modification by [22].

90 **2.3.2. Animal grouping and treatment**

91 The animals were divided into five (5) groups each comprised of six (6) male rats.
92 Four groups were induced with BPH which were grouped as group I to group IV). Groups I
93 and II received 50 and 100mg kg⁻¹ body weight (bw) of *Ocimum gratissimum* extract; group
94 III received finasteride (orthodox drug) at 0.1mg kg⁻¹; all by gavages for thirty five days,
95 group IV was left untreated for thirty five days before sacrifice to assess possible reversal of

the exogenous induction and group 5 served as normal control. The animals were weighed prior to the commencement of the experiment and subsequently every week till the end of the experiment.

2.4. Determinations of Biochemical Parameters

After 35 days, the rats were anaesthetized by a brief exposure to trichloromethane vapour and bled by cardiac puncture. The sera were carefully separated and used for the determination of various biochemical analyses. Each rat's carcass was promptly dissected and the prostates were carefully excised. The prostates were freed of external fascias, washed in cold normal saline, blotted with filter paper and weighed on a sensitive balance.

3.5. Determination of total cholesterol, High density lipoprotein (HDL-cholesterol) and Triacylglycerol determination

Determination of total cholesterol, high density lipoprotein (CHOD-PAP method) as described by [23] while Triacylglycerol (GPO-PAP method) as described by [24]. Low density lipoprotein was determined as described by [25]. All were done using Randox assay kits.

3.6. Statistical Analysis

The experimental data were analysed for statistical significance by one-way analysis of variance and post hoc comparison using the SPSS version. All data were reported as mean $\pm$ SD and statistical significance was accepted at $P < 0.05$.

4.0 Results

4.1. Body weight

The effect of oral administration of extract and finasteride on body weight is shown in Table 1. The BPH-control group exhibited a decline in body weight when compared with normal control. The extract and standard drug (finasteride) treated groups exhibited an increase in body weight when compared with the BPH control group. Administration of extract or standard drug (finasteride) improved the body weight near normal level when compared with normal control.

4.2. Prostate weight

The weight of the prostates was at the highest in the BPH control group when compared with normal control group (Table 1). BPH control group exhibited a significant ($P < 0.05$) increase in prostate weight when compared to normal control. The extract and standard drug treated groups showed a decrease in prostate weight when compared with the BPH-control group.

4.3. Serum cholesterol concentration of BPH-induced rats

There was a significant ($P < 0.05$) rise in the serum cholesterol level in BPH control group when compared with the treated groups. In all the treated groups there was an improved reduction of serum cholesterol levels when compared to the BPH control group.

4.4. Serum triacylglycerol (TG) concentration of BPH-induced rats

The results indicate that there was a significant reduction in the TG concentration in the OG treated and standard drug treated groups when compared the BPH control group.

4.5. High density lipoprotein (HDL-c) concentration of BPH induced rats

A significant ($P < 0.05$) decrease in the serum HDL-C level in BPH control group was observed when compared with the treated groups. In all the treated groups there was an increase in serum HDL-C concentrations when compared to the BPH control group.

4.6. Serum low density lipoprotein (LDL-c) concentrations of BPH induced rats

There was a significant ($P < 0.05$) rise in LDL-C level of BPH control group when compared with the treated groups. Treatment with the extract showed a significant decline in the levels of LDL concentrations when compared to the BPH control.

Table 1: Effect of extract of OG and finasteride body weight and prostate weight

GROUP	BODY WEIGHT (g)	PROSTATE WEIGHT (g)
BPH + 50mg OG	254.30±7.22 ^b	0.70±0.30 ^{ab}
BPH + 100mg OG	267.70±8.60 ^b	1.00±0.40 ^b
BPH + FINASTERIDE	270.30±7.98 ^c	0.53±0.22 ^{ab}
BPH CONTROL	220.30±7.92 ^a	2.11±0.27 ^c
NORMAL CONTROL	272.10±7.90 ^c	0.31±0.06 ^a

Values are expressed as Mean ± SD. Benign prostate hyperplasia (BPH), *Ocimum gratissimum* (OG). Non- identical superscripts (i.e. a, b, c) means there is significance between the comparing groups at $P < 0.05$.

Table 2: Effect of extracts of OG and finasteride on serum lipid profile

GROUP	CHOLESTEROL (mg/dl)	TRIACYL-GLYCEROL (mg/dl)	HDL-c (mg/dl)	LDL-c (mg/dl)	VLDL-c (mg/dl)
BPH + 50mg OG	147.70±3.93 ^{bcd}	70.00±1.20 ^b	59.78±3.18 ^a	12.27±3.93 ^{ab}	15.20±0.26 ^b
BPH + 100mg OG	146.46±3.42 ^{bcd}	69.24±1.75 ^b	60.81±4.07 ^a	11.58±1.98 ^{ab}	15.05±0.37 ^b
BPH + FINASTERIDE	155.00±6.93 ^{cd}	68.37±5.04 ^b	60.73±1.57 ^a	15.85±3.59 ^{bc}	14.88±1.03 ^b
BPH CONTROL	175.82±11.81 ^c	76.12±5.32 ^c	79.78±3.86 ^b	22.27±12.35 ^c	16.43±1.08 ^c
NORMAL CONTROL	131.78±4.89 ^a	61.37±1.52 ^a	63.32±1.64 ^a	7.35±2.69 ^a	13.48±0.32 ^a

Values are expressed as Mean ± SD. Benign prostate hyperplasia (BPH), High density lipoprotein (HDL), Low density lipoprotein (LDL), *Ocimum gratissimum* (OG). Identical superscript (i.e. a) means there is no significant difference between the comparing group

$P > 0.05$. Non- identical superscripts (i.e. a, b, c, d, e) means there is significance between the comparing groups at $P < 0.05$.

Discussion

In the prostate gland, lipids promote the cellular proliferation, contractility and overall enlargement of the prostate and thus represent a potential risk factor for BPH and prostate cancer [26, 27]. The prostate is a cholesterol-rich tissue; therefore elevated serum cholesterol may result in the accumulation of cholesterol in the cell membrane forming large lipid rafts [28]. These lipid rafts have been shown to have pro-carcinogenic cell signalling effects that will result in the enlargement of prostate.

Some data point out that modifiable risk factors of cardiovascular disease might raise the risk of BPH and contribute to its development. Obesity [7, 29, 30, 31] elevated fasting plasma glucose levels [32, 33] diabetes [10], and the metabolic syndrome, have been linked to cause an increased risk of BPH and male LUTS. Anomalous in concentrations of lipids and lipoproteins are well-proved risk factors for cardiovascular disease, and include elevated serum low density lipoprotein cholesterol, decreased serum high-density lipoprotein (HDL-c), and increased serum triglycerides. These factors make-up the metabolic syndrome and often arise in association with other cardiovascular risk factors, including diabetes. This observation raises the likelihood that abnormal lipids and lipoproteins might also be linked to the cause of BPH [34].

Some researchers [35] observed that prostate weight was significantly higher in hyperlipidemic rats than in controls. The increased prostate weight is used as one of crucial markers of BPH according to previous study [36, 37]. BPH is characterized by stromal and epithelial cells hyperplasia, resulting in prostate enlargement. In previous studies, animals with BPH had a significant increase in prostate weight compared with normal control animals, whereas those of animals treated with finasteride or others herbal remedies for the

180 management of BPH had significantly reduced the weight compared with BPH animals [36,
181 38, 39]

182 In a subsequent report, some researchers [40] observed that men with BPH had
183 significantly higher total cholesterol and low-density lipoprotein (LDL) cholesterol levels
184 than did men without BPH. Obesity and dyslipidemia have been well reported to increase risk
185 of BPH and high grad CaP [11, 41].

186 The estimation of lipid profile indicated that the extract was capable of reducing the
187 concentrations of cholesterol, triacylglycerol, low density lipoprotein and very low density
188 lipoprotein in the treated rats. Some pervious researches indicated similar progression [3, 42].
189 Total-cholesterol and low-density lipoprotein have been established to be significantly high
190 in BPH patients compared to normal person [40]. It has been established that the amount of
191 body fat found in males increases as one gets older [43]. It is likely that the increase amount
192 of body fat as a result of increased age can join to increase the development and progression
193 of BPH.

194 Increase in concentrations of cholesterol, triacylglycerol, low density lipoprotein and
195 very low density lipoprotein and decrease in high density lipoprotein in BPH control group
196 implies lipid metabolism is implicated in BPH condition. Treatment with extract was able to
197 attenuate this alteration in lipid metabolism. It therefore means that reduction of the body fat
198 is crucial in improving the management of BPH. This study indicates that *Ocimum*
199 *gratissimum* has the capacity to control the metabolism of lipid which can very helpful in the
200 management of benign prostate hyperplasia.

201 **Conclusion**

202 The assessment of lipid profile indicated that the extract was capable of reducing the
203 concentrations of cholesterol, triacylglycerol, low density lipoprotein and very low density

lipoprotein in the treated rats. As it has been established, that lipids can promote cellular proliferation, contractility and overall enlargement of the prostate gland. It is therefore logical to suggest that reduction of lipid component of the body will go a long way in management of benign prostatic hyperplasia.

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