

1 **Evaluation** of *Ocimum gratissimum* leaf Extract on Lipid
2 **Profile of Experimentally-Induced** Prostatic Hyperplasia
3 **Animal Model**
4

5
6 **Abstract**

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

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

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

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

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

27 **1. Introduction**

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

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

48 Scientific evaluation of medicinal plants is important to the discovery of novel drugs
49 and also helps to assess toxicity risks associated with the use of either herbal preparations or
50 conventional drugs of plant origin.

51 Some studies have established the 5 α -reductase inhibitory activities of certain herbs
52 such as *Ganoderma lucidum*, *Urtica dioica*, *Caesalpinia bonducella*, *Tribulus terrestris*,
53 *Pedaliium murex*, *Sphaeranthus indicus*, *Cuscuta reflexa*, *Citrullus colocynthis*, *Benincasa*
54 *hispida*, *Phyllanthus niruri*, *Echinops echinatus*, *Pygeum africanum* and *Hypoxis rooperi*,
55 confirming that they are useful in the management of androgenic disorders which include
56 BPH [1, 2, 18, 19, 20, 21, 22, 23]. Several studies have established the usefulness of herbal
57 medicine in the management of BPH [2, 20, 24]. Previous reports on phytotherapeutic
58 management of BPH established the inhibitory effect of *Lepidium meyeri* extract [25] and
59 protective effect of *Echinops echinatus* and *Ganoderma lucidum* extracts [20, 21] on
60 testosterone induced BPH. *Benincasa hispida* Congn., *Sphaeranthus indicus*, *Abrus*
61 *precatorious* and *Urtica dioica* were reported to inhibit 5-alpha reductase enzyme activity [1,
62 26] and these plants have demonstrated ameliorative effect on testosterone-induced prostate
63 hyperplasia by reducing relative prostate weight in treated animals [1, 22, 23]. *Seronoa*
64 *repens* also known as saw palmetto contains sterols and its inhibitory effect on 5-alpha
65 reductase activity with attendant decrease in DHT production has been reported to be useful
66 in the management of [27]. Peng *et al.* [28] established that antrodan, a β -glucan obtained
67 from *Antrodia cinnamomea mycelia*, is helpful in managing benign prostate hyperplasia.

68 *Ocimum gratissimum* contain different compounds such as alkaloids, saponins,
69 tannins, anthraquinone, flavonoids, steroids, terpenoids and cardiac glycosides [29, 30, 31]
70 which makes it useful in traditional medication. This study investigated the usefulness of the
71 leaf extract of *Ocimum gratissimum* in the management of the experimentally hormone-
72 induced BPH in Wistar rats and its effect on lipid metabolism. The results will contribute to

73 the search for locally available phytotherapeutic agents that can help in managing this
74 debilitating disease especially in among the poor ones.

75 **2. Materials and Methods**

76 **2.1. Plant Material**

77 Fresh leaves of *Ocimum gratissimum* were harvested from a garden in Okuku in Yala
78 Local Government of Cross River State, South-South, Nigeria. The plant was identified and
79 authenticated by Dr. Michael Eko, a botanist in the Department of Biological Sciences,
80 University of Calabar and a voucher specimens number 431 deposited in a herbarium in the
81 Department of Botany. Their fresh leaves were washed and dried under the shade for seven
82 days. The dried leaves were pulverized using pestle and mortar to get a powder that was used
83 for extraction.

84 **2.1.1. Preparation of extract**

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

89 **3.0 Hormones**

90 Testosterone propionate Brand name: Ricostrone; a product of Greenfield pharma,
91 Jiangsu Co Ltd., China. Estradiol valerate (by Medipharma Ltd., 108-Kotlakhpat industrial
92 Est; Lahore, India. Testosterone propionate (T) and estradiol valerate E₂ (puregynon depot)
93 were used for the induction of prostate enlargement at doses of 400µg T and 80µg E₂ [32]
94 respectively. This was administered to the rats for three weeks subcutaneously in the inguinal

95 region. All Chemicals used in this study were of analytical grade and were obtained from
96 reputable companies.

97 **3.1. Animals**

98 A total of thirty (30) Wistar rats weighing between 200-300g were obtained from the
99 animal house of the Faculty of Basic Medical Sciences, Cross River University of
100 Technology, Okuku Campus, Nigeria. The rats were used for the experiment. The rats were
101 acclimatized for two weeks before the experiment commences. The rats were exposed to
102 approximately 12-hour light/dark cycles under humid tropical conditions, given tap water and
103 feed *ad libitum*, and were housed in standard plastic cages (five per cage) throughout the 35-
104 day duration of the study. The animal room was well be ventilated with a temperature range
105 of 27-29 °C. The Institutional Animal Ethics Committee, Cross River University of
106 Technology, Calabar, Nigeria, (IAEC/CRUTECH/17/083) approved the study before the
107 experiment and certified all experimental protocols.

108 **2.3.1. Induction of BPH**

109 BPH was induced by exogenous administration of testosterone and estradiol in
110 staggered doses three times a week respectively for three weeks. The hormones were diluted
111 with corn oil which served as the solvent. The dilution was done by taken 19 mL of corn oil
112 and adding it to 1 mL (25 mg) of testosterone to form a 20 mL stock solution while 24 mL of
113 corn oil was added to 1 mL of estradiol to make up a stock solution of 25 mL. From the stock
114 solutions prepared, 200g rat was injected with 400 µg of testosterone and 80 µg of estradiol
115 separately at the different thighs [32] with modification by Mbaka *et al.* [33].

116 **2.3.2. Animal grouping and treatment**

117 The animals were divided into five (5) groups each comprised of six (6) male rats.
118 Four groups were induced with BPH which were grouped as group I to group IV). Groups I
119 and II received 50 and 100mg kg⁻¹ body weight (bw) of *Ocimum gratissimum* extract; group
120 III received finasteride (orthodox drug) at 0.1mg kg⁻¹; all by gavages for thirty five days,
121 group IV was left untreated for thirty five days before sacrifice to assess possible reversal of
122 the exogenous induction and group 5 served as normal control. The animals were weighed
123 prior to the commencement of the experiment and subsequently every week till the end of the
124 experiment.

125 Table 1: Animal grouping and treatment (Daily for 35 days)

GROUP	TREATMENT
I	BPH + 50 mg/kg OG
II	BPH + 100 mg/kg OG
III	BPH + 0.1 mg/kg of FINASTERIDE
IV	BPH CONTROL
V	NORMAL CONTROL

126

127 2.4. Determinations of Biochemical Parameters

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

3.4.1 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 the National Cholesterol Education Program (NCEP) [34] while Triacylglycerol (GPO-PAP method) as described by Tietz [35]. Low density lipoprotein was determined as described by Assmann [36]. All were done using Randox assay kits.

3.5. 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

Table 2: Effect of extract of OG and finasteride body weight, prostate weight and prostate/body weight ratio

GROUP	BW (g)	PW (mg)	P/BW ratio (mg/g)
BPH + 50mg OG	254.30 $\pm$ 7.22 ^b	700 $\pm$ 300.00 ^{ab}	2.75 $\pm$ 0.04 ^c
BPH + 100mg OG	267.70 $\pm$ 8.60 ^b	1000 $\pm$ 400.00 ^b	3.74 $\pm$ 0.05 ^c
BPH + FINASTERIDE	270.30 $\pm$ 7.98 ^c	530 $\pm$ 220.00 ^{ab}	1.96 $\pm$ 0.03 ^b
BPH CONTROL	220.30 $\pm$ 7.92 ^a	2110 $\pm$ 270.00 ^c	9.58 $\pm$ 0.07 ^d
NORMAL CONTROL	272.10 $\pm$ 7.90 ^c	310 $\pm$ 60.00 ^a	1.14 $\pm$ 0.1 ^a

Values are expressed as Mean $\pm$ SD. Benign prostate hyperplasia (BPH), *Ocimum gratissimum* (OG), Body weight (BW), Prostate weight (PW), Prostate/body weight (P/BW) ratio. Non- identical superscripts (i.e. a, b, c) means there is significance between the comparing groups at $P < 0.05$.

4.1. Effect of extract of OG and finasteride on body weight, prostate weight and prostate/body weight ratio

The effect of oral administration of extract and finasteride on body weight is shown in Table 2. 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.

The weight of the prostates and prostate/body weight ratio were at the highest in the BPH control group when compared with normal control group (Table 2). BPH control group exhibited a significant ($P < 0.05$) increase in prostate weight and prostate/body weight ratio when compared to normal control. The extract and standard drug treated groups showed a decrease in prostate weight and prostate/body weight ratio when compared with the BPH-control group.

Table 3: Effect of extract 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 $P < 0.05$.

4.2. Lipid Profile

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.

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. 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.

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 3).

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 [37, 38]. 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 [39]. 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, 40, 41, 42] elevated fasting

195 plasma glucose levels [43, 44] diabetes [10], and the metabolic syndrome, have been linked
196 to cause an increased risk of BPH and male LUTS. Anomalous in concentrations of lipids and
197 lipoproteins are well-proved risk factors for cardiovascular disease, and include elevated
198 serum low density lipoprotein cholesterol, decreased serum high-density lipoprotein (HDL-
199 c), and increased serum triglycerides. These factors make-up the metabolic syndrome and
200 often arise in association with other cardiovascular risk factors, including diabetes. This
201 observation raises the likelihood that abnormal lipids and lipoproteins might also be linked to
202 the cause of BPH [45].

203 Some researchers [46] observed that prostate weight was significantly higher in
204 hyperlipidemic rats than in controls. The increased prostate weight is used as one of crucial
205 markers of BPH according to previous study [47, 48]. BPH is characterized by stromal and
206 epithelial cells hyperplasia, resulting in prostate enlargement. In previous studies, animals
207 with BPH had a significant increase in prostate weight compared with normal control
208 animals, whereas those of animals treated with finasteride or others herbal remedies for the
209 management of BPH had significantly reduced the weight compared with BPH animals [47,
210 49, 50]

211 In a subsequent report, some researchers [51] observed that men with BPH had
212 significantly higher total cholesterol and low-density lipoprotein (LDL) cholesterol levels
213 than did men without BPH. Obesity and dyslipidemia have been well reported to increase risk
214 of BPH and high grad CaP [11, 52].

215 The estimation of lipid profile indicated that the extract was capable of reducing the
216 concentrations of cholesterol, triacylglycerol, low density lipoprotein and very low density
217 lipoprotein in the treated rats. Some pervious researches indicated similar progression [3, 53].
218 Total-cholesterol and low-density lipoprotein have been established to be significantly high

in BPH patients compared to normal person [51]. It has been established that the amount of body fat found in males increases as one gets older [54]. It is likely that the increase amount of body fat as a result of increased age can join to increase the development and progression of BPH.

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

Conclusion

The assessment of lipid profile indicated that the extract was capable of reducing the 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.

Consent: NA

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