



Evaluation of Impact of Some Selected Plants on Haematological Parameters of Testosterone and Estradiol Induced Benign Prostatic Hyperplasia Adult Male Rats

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Authors' contributions

This work was carried out in collaboration author all authors. Authors MNU and AAA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MNU and MUE managed the analyses of the study. Author EOE managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Benign prostate hyperplasia (BPH) is an age-related disease of unknown etiology, characterized by prostate enlargement. The effect of *Prosopis africana* (PA), *Vernonia amygdalina* (VA) and *Ocimum gratissimum* (OG), plant extracts on haematological parameters of BPH animal model was investigated.

Methods: BPH was induced in 45 male Wistar rats (250-350 g) by exogenous injection of testosterone and estradiol in staggered doses for 3 weeks. To confirm BPH induction, some animals

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were sacrificed; histological inspection of prostate gland and PSA was carried out. Forty BPH induced rats were divided into 8 groups. Group 1 and 2, 3 and 4, 5 and 6 were treated with 50 mg/kg bw and 100 mg/kg bw doses of PA, VA and OG extracts respectively. Group 7 received finasteride (0.1 mg/kg bw). Group 8 BPH control and five rats without induction constitute group 9, the normal control and both received distilled water. After 45 days, the rats were anaesthetised by a brief exposure to trichloromethane vapour and 5 ml of blood was collected from the rats through cardiac puncture and dispensed into well-labelled EDTA containers to avoid coagulation. All analyses were completed within 24 h of sample collection.

Results: Results showed that induction of BPH caused a significant ($P < 0.05$) enlargement of prostate gland when compared to normal control. All extracts produced significant ($P < 0.05$) reduction in the weight of the enlarged prostate when compared to the BPH control. There were significant ($P < 0.05$) decline in RBC, PCV and Hb of BPH control when compared to the normal control and treated groups. In the treated groups the administration of the extracts and standard drug exhibited an increase in RBC, PCV and Hb concentration when compared with the BPH control. Also there was significant ($P < 0.05$) increase in the WBC, neutrophils, platelets, monocytes, lymphocytes and eosinophils levels in BPH control when compared to normal control and treated groups. In all treated groups there was significant decrease in WBC, neutrophils, platelets, monocytes, lymphocytes and eosinophils concentration levels when compared with the BPH control group.

Conclusion: The result of this study indicates that the extracts have the potential to reverse the inflammation caused by BPH and also have the capacity to boost the numbers of red blood cells probably by inhibiting the hemolysis caused by inflammatory factors or by enhancing the production of red blood cell from the bone marrow.

Keywords: *Prosopis africana*; *Vernonia amygdalina* and *Ocimum gratissimum*; prostate disorder; haematology.

1. INTRODUCTION

The prostate gland is a major secondary endocrine organ of males whose development and growth depends on androgen stimulation especially by dihydrotestosterone (DHT). It is shown that androgen and estrogens constitute the primary factors responsible for prostate diseases [1,2,3,4]. Aging is associated with increased accumulation of DHT which results in increased cell growth and hyperplasia [5]. Benign prostatic hyperplasia (BPH) is a common non-malignant urologic condition among older man which is characterized by prostate enlargement, bladder outlet obstruction (BOO), and lower urinary tract symptoms (LUTS).

In orthodox medical practice, various medications such as alpha-adrenergic blockers and 5 alpha-reductase inhibitors have been used successfully to manage the lower urinary tract symptoms associated with prostate hyperplasia [6]. In addition to refractory retention of urine (repeated urine retention) other complications from benign prostate hyperplasia such as haematuria, recurrent urinary tract infections, bladder calculi and renal insufficiency are managed with surgical interventions such as open prostatectomy and transurethral resection of the prostate [7].

Currently alternate medicine has been incorporated into the main stream medical services. As a result, more patients are resorting to Traditional Medicine to address their ailments including prostate conditions [6]. Other reasons for the increase in herbal medicine use in underdeveloped countries has been attributed to such factors as the high cost of pharmaceutical medicines and overcrowding of patients in clinics and hospitals [8]. Herbal medicine, botanical medicine or phytomedicine refers to using plant components such as seeds, berries, roots, leaves, bark, or flowers for medicinal purposes [9]. It has been noted that Traditional Medical practice has long been used outside of conventional medicine but mainly for primary health care [6].

The use of herbal medicine has been reported to be on the increase in many developing and industrialized countries [10,11]. The World Health Organization (WHO) estimates that four billion people (about 80 percent of the world population) use herbal medicine for some aspect of primary health care [12,13,14]. Previous study by Ugwu, et al. [15] has established that *Ocimum gratissimum* was effective in reducing high levels of PSA, prolactin, testosterone, estradiol values and prostate weight caused as a result of BPH in a rat model. Ugwu, et al. [16] has demonstrated

that treatment of BPH animal model with *Prosopis africana* seed extract for 45 days significantly inhibited the development of induced prostatic hyperplasia, which was evident in the reduction in the elevated prostate weight, reduced prostatic specific antigen (PSA), testosterone, estradiol and prolactin levels in the serum. The increased prostate weight is used as one of crucial markers of BPH according to previous study [17,18]. Also, Ugwu, et al. [19] has proven that administration of the aqueous extract of *Vernonia amygdalina* to rats induced with BPH has protective effects against the development of BPH as seen in the reduction in PSA levels, prostate weight, improved prostate histological patterns. It has been established that serum PSA levels increase abnormally in patients with benign prostatic hyperplasia and prostatitis [20]. Therefore reduction of the serum PSA level can show protective effects on benign prostatic hyperplasia.

The practice of traditional medicine is as old as the origin of man [21]. The use of plants in traditional medicine referred to as herbalism or botanical medicine [22] falls outside the mainstream of the Western or Orthodox medicine. It has been estimated that about two third of the world's population (mainly in the developing countries) rely on traditional medicine as their primary form of health care. The use of traditional medicine in the treatment and management of diseases in the African continent cannot fade away and this could be attributed to the socio-cultural, socio-economic, lack of basic health care and qualified personnel [23]. Plants contain active components such as anthraquinones, flavonoids, glycosides, saponins, tannins, etc., which possess medicinal properties that are harnessed for the treatment of different diseases. Many studies reported that oral ingestion of medicinal drugs can alter the haematological parameters ranges to either positive or negative [24,25]. There is paucity of data on relationship between haematological parameters and BPH. Therefore it is paramount to study the effect of these three indigenous plants on haematological parameters in BPH condition.

Haematology refers to the study of the number and morphology of the cellular elements of blood particularly; the red blood cells (erythrocytes), white blood cells (leucocytes) and the platelets (thrombocytes) in addition to the use of these results in the diagnosis and monitoring of diseases [26]. Haematological studies are of

ecological and physiological interest in helping to understand the relationship of blood characteristics to the environment [27]. Evaluation of blood parameters can be used to determine the level of negative effect of foreign compounds, including medicinal plants [28,29, 30]. This method can also be used to explain haematological relating functions of plant products [31]. In addition, such investigation is necessary to risk examination as changes in the blood system have higher predictive value on human toxicity when data are explained from animal studies [24].

Blood transports nutrients and oxygen to body cells and removes waste products away from the cells [32]. It is a composite of erythrocytes, leucocytes, thrombocytes, plasma and accounts for 7% of human body weight [33]. Oxygen distribution to the periphery from the lungs through the pulmonary capillaries, removal of carbon dioxide from the tissues back to the lungs through the systemic capillaries and maintenance of acidic and basic values of the body are the three main functions of erythrocytes [34].

Leucocytes are the main cells of the immune system that provide innate and specific adaptive immunity. They are further divided into five different classes which include; basophils, neutrophils, eosinophils, lymphocytes and monocytes [35]. Platelets play a major role in hemostasis, thrombosis, clot retraction, vessel constriction and repair, inflammation including promotion of atherosclerosis, host defense and even tumor growth/metastasis [36]. Haematological complications consist mainly of abnormalities in the function, morphology and metabolism of erythrocytes, leucocytes and platelets [37,38]. Hence the need to study the effect of these three plants on haematological parameters in benign prostate hyperplasia condition.

2. MATERIALS AND METHODS

2.1 Plant Material I and II: *Ocimum gratissimum* and *Vernonia amygdalina*

Fresh leaves of *Ocimum gratissimum* and *Vernonia amygdalina* were harvested from a garden in Okuku in Yala Local Government of Cross River State, South-South, Nigeria. The plants were identified at the herbarium unit of the Department of Biological Sciences, University of

Calabar. Their fresh leaves were washed with clean water and dried under the shade for six days. Their dried leaves were milled using pestle and mortar to get powders that were used for extraction.

2.1.1 Preparation of extracts of *Ocimum gratissimum* and *Vernonia amygdalina*

The powdered sample of *Ocimum gratissimum* and *Vernonia amygdalina* 100 grams were soaked into 100 ml of distilled water separately. These were filtered after 48 hours and filtrate were concentrated in hot air oven. The solutions were diluted with corn oil, to produce a solution 100 mg/ml respectively. Administrations of extracts were totally by gavage. Proper concentrations were administered by the use of oropharyngeal canula and calibrated hypodermic syringe.

2.2 Plant Material III: *Prosopis africana*

Prosopis seeds were purchased from Shibori market in Ogoja Local Government of Cross River State, Nigeria. The seeds (500 g) was sorted, cleaned and was boiled for 5 h using a gas cooker and allowed to cool to room temperature. The boiling helps to soften the hulls for easy removal and separation of the cotyledons. After it was dehulled and decorticated. The dehulled and boiled seeds were washed again with clean water. The processing of decortications was done by hand squeezing the seeds and washing with clean water. The wet decorticated seeds were kept in a large polythene sacks to exclude air and was fermented for three days according to the method described by Achi [39]. The fermentation was done at room temperature ($\approx 25^{\circ}\text{C}$) for 72 h. The fermented seeds were then sun-dried to a constant weight and milled using hammer mill to produce *prosopis* seed flour [40]. The flour was kept in a refrigerator at 4°C prior to use.

2.3 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 gland enlargement at a dose of $400\ \mu\text{g T}$ and $80\ \mu\text{g E2}$ [41]. This was administered to the rats for three

weeks subcutaneously in the inguinal region after which a few rats were sacrificed and inspected for gross examination of prostate gland enlargement. All Chemicals used in this study were of analytical grade and were obtained from reputable companies.

2.4 Animals

A total of fifty (50) Wistar rats weighing between 250-350 g were obtained from the animal house of the Faculty of Basic Medical Sciences, University of Calabar, Nigeria. The rats were used for the experiment. The rats were acclimatized for two weeks before the experiment commences. The rats were exposed to approximately 12-hour light/dark cycles under humid tropical conditions, given tap water and feed *ad libitum*, and were housed in standard plastic cages (five per cage) throughout the 45-day duration of the study. The animal room was well ventilated with a temperature range of $27-29^{\circ}\text{C}$.

2.5 Induction of BPH

BPH was induced by exogenous administration of testosterone and estradiol in staggered doses (three times a week respectively) for three weeks according to Bernoulli, [41] with modification by Mbaka, et al. [42].

2.6 Animal Grouping and Treatment

The rats were separated into nine (9) groups each made up of five (5) male rats. Forty-five (45) rats were induced with BPH which were grouped as group 1 to group 8 and remaining 5 which were randomly selected and used to confirm the induction of BPH. Groups 1 and 2 received 50 and $100\ \text{mg kg}^{-1}$ body weight (bw) of *Prosopis africana* extract; groups 3 and 4 received 50 and $100\ \text{mg kg}^{-1}$ body weight (bw) of extract of *Vernonia amygdalina*, groups 5 and 6 received 50 and $100\ \text{mg kg}^{-1}$ body weight (bw) of extract of *Ocimum gratissimum*, group 7 received finasteride (orthodox drug) at $0.1\ \text{mg kg}^{-1}$; all by oral gavage for eight weeks. Group 8, the BPH control group was given vehicle (distilled water) for the 45-days prior to sacrifice to evaluate for likely reversal of the exogenous induction and group 9 served as normal control. The doses were based on the ones used in previous studies and $0.1\ \text{mg/kg bw}$ for finasteride was derived from the dose used in humans. The weights of the rats were measured before the initiation of the research and consequently every week till the termination of the experiment.

2.7 Sample Collection

After 45 days, the rats were anaesthetised by a brief exposure to trichloromethane vapour and 5ml of blood was collected from the rats through cardiac puncture and dispensed into well-labeled EDTA containers to avoid coagulation. All analyses were completed within 24 h of sample collection.

2.8 Haematological Assays (Full Blood Count)

Whole blood was used to determine the full blood count parameters and all the analysis were performed using standard diagnostic Diatro reagents (Diatro-Lyse-Diff, Diatro Cleaner, Diatro Diluent reagents) using Abacus junior haematology analyzer (Diatron. GmbH. Wein Austria). These were done according to manufacturer's instructions.

2.9 Statistical Analysis

The experimental data were analysed for statistical significance by one-way analysis of variance and post hoc comparison using the SPSS version. The Independent Samples t-test was used to compare the means of two independent groups. All data were reported as mean \pm SD and statistical significance was accepted at $P < 0.05$.

3. RESULTS

3.1 Haematological Parameters

Results showed that induction of BPH caused a significant ($P < 0.05$) enlargement of prostate gland when compared to normal control. All

extracts produced significant ($P < 0.05$) reduction in the weight of the enlarged prostate when compared to the BPH control (Table 1).

Results of red blood cells (RBC) count, packed cell volume (PCV), haemoglobin (Hb) concentration, white blood cells (WBC) count, neutrophils, platelets, monocytes, lymphocyte, eosinophils and basophils concentration for the treated and control groups are shown in Tables 2, 3 and 4.

There were significant ($P < 0.05$) decline in RBC, PCV and Hb of BPH control when compared to the normal control and treated groups. In the treated groups the administration of the extracts and standard drug exhibited an increase in RBC, PCV and Hb concentration when compared with the BPH control.

There were significant ($P < 0.05$) increases in the WBC, neutrophils, platelets, monocytes, lymphocytes and eosinophils levels in BPH control when compared to normal control and treated groups. In all treated groups there were significant decreases in WBC, neutrophils, platelets, monocytes, lymphocytes and eosinophils concentration levels when compared with the BPH control group.

4. DISCUSSION

Benign prostatic hyperplasia is caused by changes in hormone balance and consequently in cell growth, but molecular pathways leading to this condition are still largely unknown. Inflammatory component is believed to have an important role while presence and degree of inflammation corresponds to prostate volume and weight [43,44]. The origin of inflammation in the prostate remains a subject of

Table 1. Effect of extract of PA, VA, OG and finasteride body weight and prostate weight

| Group | Body weight (g) | Prostate weight (g) |
|-------------------|---------------------------------|-------------------------------|
| BPH + 50 mg PA | 286.80 \pm 8.41 ^b | 0.97 \pm 0.33 ^b |
| BPH + 100 mg PA | 311.20 \pm 5.45 ^c | 0.85 \pm 0.41 ^{ab} |
| BPH + 50 mg VA | 317.60 \pm 5.27 ^c | 0.83 \pm 0.52 ^{ab} |
| BPH + 100 mg VA | 321.60 \pm 5.68 ^d | 0.72 \pm 0.36 ^{ab} |
| BPH + 50 mg OG | 304.40 \pm 8.23 ^c | 0.80 \pm 0.31 ^{ab} |
| BPH + 100 mg OG | 317.80 \pm 9.60 ^c | 1.01 \pm 0.41 ^b |
| BPH + Finasteride | 320.40 \pm 8.99 ^d | 0.63 \pm 0.23 ^{ab} |
| BPH Control | 270.40 \pm 8.93 ^a | 2.21 \pm 0.28 ^c |
| Normal Control | 322.20 \pm 13.99 ^d | 0.41 \pm 0.071 ^a |

Values are expressed as Mean \pm SD. Benign prostate hyperplasia (BPH), *Prosopis africana* (PA), *Vernonia amygdalina* (VA) and *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) means there is significance between the comparing groups at $P < 0.05$

Table 2. Effects of extracts PA, VA, OG and finasteride on haematological parameters

| Group | Rbcs ($10^{12}/l$) | Pcv (%) | Hb (g/dl) |
|-------------------|-------------------------|-------------------------|-------------------------|
| BPH + 50 mg PA | 8.47±0.38 ^{ab} | 43.35±0.70 ^a | 14.23±0.36 ^a |
| BPH + 100 mg PA | 8.50±0.49 ^{ab} | 43.38±0.73 ^a | 14.27±0.37 ^a |
| BPH + 50 mg VA | 8.45±0.26 ^{ab} | 43.44±0.67 ^a | 14.46±0.37 ^a |
| BPH + 100 mg VA | 8.80±0.22 ^b | 43.57±1.05 ^a | 14.52±0.27 ^a |
| BPH + 50 mg OG | 8.59±0.26 ^{ab} | 43.37±0.74 ^a | 14.28±0.44 ^a |
| BPH + 100 mg OG | 8.58±0.47 ^{ab} | 43.40±0.66 ^a | 14.28±0.54 ^a |
| BPH + Finasteride | 8.61±0.36 ^{ab} | 43.58±1.16 ^a | 14.29±0.39 ^a |
| BPH Control | 8.24±0.44 ^a | 38.71±1.57 ^b | 12.98±0.21 ^b |
| Normal Control | 8.86±0.06 ^b | 43.68±0.50 ^a | 14.31±0.38 ^a |

Values are expressed as Mean ± SD. Red blood cells (RBC), Packed cell volume (PCV), Haemoglobin concentration (Hb), Benign prostate hyperplasia (BPH), *Prosopis africana* (PA), *Vernonia amygdalina* (VA) and *Ocimum gratissium* (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) means there is significance between the comparing groups at $P < 0.05$

Table 3. Effects of extract PA, VA, OG and finasteride on haematological parameters

| Group | wbc ($\times 10^9/l$) | Neutrophils (%) | Platelets ($\times 10^9/l$) |
|-------------------|-------------------------|-------------------------|-------------------------------|
| BPH + 50 mg PA | 17.21±0.72 ^b | 26.24±0.63 ^b | 902.52±23.49 ^c |
| BPH + 100 mg PA | 17.31±0.83 ^b | 26.27±0.62 ^b | 907.02±19.46 ^c |
| BPH + 50 mg VA | 17.27±0.40 ^b | 26.75±0.44 ^b | 925.34±67.49 ^c |
| BPH + 100 mg VA | 17.35±0.23 ^b | 26.82±0.37 ^b | 929.81±40.01 ^c |
| BPH + 50 mg OG | 17.25±0.60 ^b | 26.39±0.70 ^b | 911.01±42.35 ^c |
| BPH + 100 mg OG | 17.31±0.69 ^b | 26.41±0.28 ^b | 914.81±54.87 ^c |
| BPH + Finasteride | 17.27±0.62 ^b | 26.50±0.48 ^b | 926.71±42.56 ^c |
| BPH Control | 24.87±0.89 ^a | 34.63±0.46 ^a | 1241.69±32.07 ^a |
| Normal Control | 17.48±0.5 ^b | 26.84±0.59 ^b | 943.98±27.00 ^b |

Values are expressed as Mean ± SD. White blood cell (WBC), Benign prostate hyperplasia (BPH), *Prosopis africana* (PA), *Vernonia amygdalina* (VA) and *Ocimum gratissium* (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) means there is significance between the comparing groups at $P < 0.05$

Table 4. Effects of extract PA, VA, OG and finasteride on haematological parameters

| Group | Monocytes (%) | Lymphocyte (%) | Eosinophils (%) |
|-------------------|----------------------------|--------------------------|------------------------|
| BPH + 50 mg PA | 17.28±0.47 ^a | 64.56±0.59 ^a | 5.62±0.56 ^a |
| BPH + 100 mg PA | 17.32±0.34 ^a | 64.66±0.63 ^{ab} | 5.77±0.25 ^a |
| BPH + 50 mg VA | 18.00±0.38 ^{bcd} | 65.55±0.43 ^{bc} | 6.01±0.31 ^a |
| BPH + 100 mg VA | 18.14±0.51 ^{cd} | 65.84±0.46 ^c | 6.14±0.36 ^a |
| BPH + 50 mg OG | 17.44±0.42 ^{ab} | 64.74±0.30 ^{ab} | 6.06±0.74 ^a |
| BPH + 100 mg OG | 17.62±0.47 ^{abc} | 64.79±0.31 ^{ab} | 6.09±0.21 ^a |
| BPH + Finasteride | 17.69±0.50 ^{abcd} | 64.85±0.30 ^{ab} | 6.18±0.26 ^a |
| BPH Control | 26.50±0.58 ^e | 72.63±1.27 ^d | 9.36±0.44 ^b |
| Normal Control | 18.31±0.37 ^d | 65.88±0.90 ^c | 6.20±0.21 ^a |

Values are expressed as Mean ± SD. Benign prostate hyperplasia (BPH), *Prosopis africana* (PA), *Vernonia amygdalina* (VA) and *Ocimum gratissium* (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 $P < 0.05$

argument and is likely to be multifactorial. It represents a chronic process of wound healing, which activates hyperproliferative programmes resulting in the formation of BPH nodules [43,44]. Acute and chronic inflammation leads to accumulation of immunocompetent cells in the prostate, mainly T lymphocytes and macrophages. However, many other cell types

may be observed, including neutrophils, eosinophils, and mast cells, depending on the type of offending agent [45]. Most of the lymphocyte populations around prostate gland are CD8+ T-lymphocytes while stroma mostly contains clusters of B-lymphocytes enclosed with CD4+ T-lymphocytes [46]. Not only lymphocytes but also stromal and epithelial

cells have cytokine receptors on membrane surface, participating in the local immune response [45, 47,48]. In a study by Cihan, et al. [49] patients with BPH had a higher level of neutrophils and lower level of mean lymphocyte count when compared to healthy individuals.

Inflammatory pathways are triggered by viral or bacterial antigens, as well as different chemical irritations and metabolic disorders. Both prostate epithelial and stromal cells and inflammatory cells produce cytokines (CCL-5, CCL-2), ILs (IL-1 α , IL-1 β , IL-6, IL-18), and hypoxia-inducible factor-1 α (HIF-1 α), creating local inflammatory microenvironment [47,50,51]. Abundant lymphoid infiltrates with a massive increase in CD4+ T-lymphocytes, as well as macrophages and mast cells, are noted in chronic prostate inflammation [52]. These cells participate in pathological changes characteristic for both BPH and prostate carcinoma. There are several studies demonstrating that ILs, which has a pro-inflammatory role, may lead to initiation and progression of BPH [45,50,51,53,54,55].

McDowell and associates showed how inflammatory cells can be attracted to the prostate tissue microenvironment and can selectively promote the proliferation of prostate epithelial cells [56]. Further studies have confirmed IL-17 to be the initiator of BPH progression *via* activation of the nuclear-factor-kappa-B (NF- κ B) pathway, which leads to secretion of other pro-inflammatory cytokines, such as IL-1, IL-6, and IL-8. Steiner, et al. [57] demonstrated that healthy prostates do not express IL-17, whereas prostates with inflammation and BPH do. Wang, et al. [58] (also found cyclooxygenase 2 (COX-2) expressed in macrophages and epithelial prostate cells within significant inflammation. Under certain conditions, if high level of T-lymphocytes is reached, surrounding cells are killed by CD8+ cytotoxic T cells and prostatic tissue is replaced by fibromuscular nodules [48,52]. Local hypoxia and inflammation also promote fibroblast to myofibroblast transformation, which leads to extracellular changes forming suitable microenvironment for continuous inflammation [47,52,59]. Inflammation is also continuously stimulated by androgens and changes within metabolic syndromes, but exact pathways are still mostly unknown [48,60, 61].

Chronic inflammation has been documented for years in benign prostatic hyperplasia (BPH). BPH is an immune inflammatory disease. Unravelling the specific nature of immune dysregulation may

help design novel drugs with these specific targets in mind [52]. Clinical evidence reported that chronic inflammation presented a key condition leading to prostate enlargement and to an increased symptoms score as well as a major risk of complications [62]. Previous study by Nickel, et al. [63] showed a positive association between inflammation and prostate volume, indeed patients with chronic inflammation at biopsy had higher volumes than those without inflammation. Robert, et al. [54] assessed the degree of prostatic inflammation using cytological and immunohistochemical parameters in 282 patients treated with surgery for complicated or symptomatic BPH.

Interestingly, the grade of prostatic inflammation was strongly associated with LUTS severity, and patients with chronic inflammation had higher, International Prostate Symptom Score (IPSS) than those without inflammation. Moreover, prostate volume was significantly higher in patients with high-grade inflammatory pattern. Burris, et al. [64] showed that LUTS improvement after radical prostatectomy correlated with degree of prostatic inflammation. The International Prostate Symptom Score (IPSS) is a short validated questionnaire which can document the baseline severity of lower urinary tract symptoms and can be used to monitor the impact of therapy. The score gives an idea of the severity of LUTS and the most bothersome symptoms. On follow-up, the score can give accurate documentation of patients' progression and deterioration [65].

Assessment of haematological parameters can be used to determine the extent of deleterious effect of foreign compounds including plant extracts on the blood constituents of an animal. Such toxicity testing is relevant to risk evaluation as changes in the haematological system have higher predictive value for human toxicity, when data are translated from animal studies [24,25]. It can also be used to explain blood relating functions of chemical compounds/plant extract [31]. Haematological analysis was carried out for *Prosopis africana*, *Vernonia amygdalina* and *Ocimum gratissimum* treated.

Red blood cells (RBC) and haemoglobin (Hb) are important in transporting respiratory gases. Haemoglobin (Hb) is contained in red blood cells and is capable of combining with oxygen in the lungs, transporting it to the tissues and releasing it there. An acute fall in Hb is usually secondary to infection induced haemolysis or an acute sequestration syndrome in the spleen (infants

and children) or liver (children and adults). Packed cell volume (PCV) is used to measure red blood cell mass and an increase in red blood cell mass is equivalent to erythrocytosis and a decrease indicates an anemia. Some medicinal plants are known to cause destruction of red blood cells leading to anaemia [66].

In this present study, RBC decreased significantly in the BPH control when compared to the treated groups. A possible explanation for the observed decrease in RBC can be linked to red cell distribution width (RDW). The red cell distribution width blood test measures the amount of red blood cell variation in volume and size. It can also help to determine the underlying cause of anemia. In previous study Patel, et al. [67] reported that BPH patients have high RDW values which reflect an underlying inflammatory state that can impair erythrocyte maturation and consequent inadequate production of the hormone erythropoietin. They further stated that undernutrition or oxidative damage can also result to this condition. Among these variables, oxidative stress and inflammation have been hypothesized as the important determinants of RDW [67]. Inflammatory states are strongly related to ineffective erythropoiesis, and it has been demonstrated that inflammatory cytokines, such as tumor necrosis factor (TNF)- α , IL-1 β and IL-6, desensitize bone marrow erythroid progenitors to erythropoiesis, inhibit red blood cell (RBC) maturation and thereby promote anisocytosis.

A decrease in the number of red cells in the blood as observed in is often associated with the development of anaemia [68]. Red blood cells (RBC) or erythrocytes, are the most common type of blood cells and the vertebrate organism's principal means of delivering oxygen (O₂) to the body tissues through the circulatory system [69]. This could be due to the stimulation of lipid peroxidative system by toxins or disease resulting in the production of lipid peroxides which haemolyse the red blood cells [70]. The decrease in haematocrit (PCV) of rats observed in the BPH control, suggests that they may induce anaemia and inability of the cells to deliver oxygen to body tissues that require them. Packed Cell Volume (PCV) or Haematocrit is used clinically to signal to known or suspected anaemia [71]. Since the purpose of red blood cells is to transfer oxygen from the lungs to body tissues; a blood sample's haematocrit can become a point of reference of its ability to deliver oxygen [71]. Factors influencing RBCs will affect the haematocrit because RBCs

comprise 99% of the total cells of the blood [71]. A lower than normal haematocrit is representative of anaemia especially the aplastic anaemia and some thalassemia syndromes [72].

In extract-treated groups, there was also a significant increase in these parameters when compared with the BPH groups. This could be due to the phytochemical constituents in the extract and also presence of minerals and vitamins. Some of these constituents are well known haemopoietic factors that have direct influence on the production of blood in the bone marrow [73,74]. The findings of this study seem to support this claim and restoration of these functions. *Prosopis africana*, *Vernonia amygdalina* and *Ocimum gratissimum* extracts seem to facilitate iron absorption, as adequate amount of this element is necessary for haemoglobin synthesis and for the animal tissues such as the kidneys and bones to take part in manufacture of RBCs.

Furthermore the increase in PCV as observed by the extracts is an indication that the extracts contain phytochemicals that can stimulate the secretion of erythropoietin—a glycoprotein hormone that stimulates stem cells in the bone marrow to produce RBCs [75]. This may be attributed to the presence of some compounds [76] and its richness in iron and vitamins [77,78, 79,80].

White blood cells (WBCs) are immune cells found in the body. White blood cells (WBCs), also called leukocytes are the cells of the immune system that are involved in protecting the body against both infectious disease and foreign invaders. Neutrophils, lymphocytes, monocytes, and eosinophils are different types of white blood cell. These cell types fight against disease and infection in the body. Neutrophils are the predominant immune cell population in human blood, where they patrol and protect the body from pathogens, and diseases [81]. Lymphocytes are white blood cells uniform in appearance but varied in function and include T, B, and natural killer cells. These cells are responsible for antibody production, direct cell-mediated killing of virus-infected and tumor cells, and regulation of the immune response [82]. Monocytes are circulating blood leukocytes that play important roles in the inflammatory response, which is essential for the innate response to pathogens. But inflammation and monocytes are also involved in the pathogenesis of inflammatory diseases [83]. Monocyte chemotactic protein-1 is secreted from prostatic

stromal cells and stimulates the proliferation of prostatic epithelial cells *in vitro* [84]. Monocyte chemotactic protein-1 might be another possible explanation of the correlation between WBC and prostate volume [84].

An increased number of WBC can occur abnormally as a result of an infection, cancer, or toxic chemical [85]. There have been reports that inflammation is a cause of prostatic enlargement [86]. So a possible explanation is that asymptomatic inflammation of the prostate may increase the WBC and the neutrophil count. Serum WBC was reportedly associated with serum monocyte chemotactic protein-1 levels [87]. Reduced WBC showed that the immune system was not compromised in animals treated with *Prosopis africana*, *Vernonia amygdalina* and *Ocimum gratissimum* which may be due to its content of immune-boosting phytochemicals. Previous studies showed similar trend [88,89,90, 91]. This signifies that these plants can help preserve the body's adaptive response to stress caused by BPH.

Eosinophils are pleiotropic multifunctional leukocytes involved in initiation and propagation of diverse inflammatory responses, as well as modulators of innate and adaptive immunity [81]. They are multifunctional leukocytes implicated in the pathogenesis of numerous inflammatory processes including parasitic helminth, bacterial and viral infections, tissue injury, tumor immunity, and allergic diseases [92,93,94]. In response to the diverse stimuli, eosinophils are recruited from the circulation into inflammatory foci where they modulate immune responses through an array of mechanisms. Triggering of eosinophils by engagement of receptors for cytokines, immunoglobulins, and complement can lead to the secretion of an array of proinflammatory cytokines, such as interleukin (IL)-2, IL-4, IL-5, IL-10, IL-12, IL-13, IL-16, IL-18, and transforming growth factor (TGF)- α/β , chemokines such as CCL5/RANTES and CCL11/eotaxin-1, and lipid mediators such as platelet-activating factor (PAF) and leukotriene (LT)C₄ [95]. These molecules have proinflammatory effects that include upregulation of adhesion systems, modulation of cellular trafficking and activation and regulation of vascular permeability, mucus secretion, and smooth muscle constriction. This could explain the observed increase in eosinophils in the BPH control group. But the extracts were able to reduce this observed increase.

Platelet is implicated in blood clotting and plays a crucial role in reducing blood loss and repair of

vascular injury [96]. The significant increase in platelet concentration in the BPH control indicates that the disease condition can stimulate the biosynthesis of blood clotting factors [97, 98]. Mean platelet volume (MPV) is a simple indicator of platelet size and has been known to be a marker of platelet activity. Some platelet markers, such as MPV, have been reported to be related to inflammation [99]. MPV is correlated with inflammation in inflammatory bowel diseases, rheumatoid arthritis, and ankylosing spondylitis, as reported in previous studies [100]. In the present study, it was identified that platelets levels increased in asymptomatic BPH rats compared with other groups. It might be possible that the elevation of platelets in asymptomatic BPH rats result from the effect of inflammation on thrombopoiesis.

The relationship between MPV values and BPH and prostatitis remain unclear. MPV is a widely used laboratory indicator associated with platelet function based on inflammatory conditions [100]. MPV also represents platelet function, which is central to processes that are involved in coronary heart disease pathophysiology and endothelial dysfunction. Platelet parameters might be influenced by coronary risk factors including age, obesity, smoking, diabetes mellitus, hypertension, hyperlipidemia, metabolic syndrome, stroke, peripheral artery disease, and deep vein thrombosis [101]. MPV can also be affected by thyroid diseases, bullous pemphigoid, malignancy, and medications such as anticoagulant therapy and statins [102,103]. Karaman, et al. [104] initially reported that MPV values significantly decreased after treatment in all grades of prostatitis and BPH.

Some plants have the capacity to boost immune cells and enhance production of red blood cells. Also literature has shown that ingestion of medicinal compounds or drugs can alter the normal range of haematological parameters [105]. Previous study by Hassan, et al. [106] has reported increase in haematological values of PCV, RBC, WBC and HB in the birds fed with decorticated fermented *Prosopis africana* seeds, this indicate that the plant may have the capacity to enhance erythropoietin release. Report by Chike, et al. [107] demonstrated that administration *V. amygdalina* brought significant reduction in the blood levels of erythrocyte parameter especially for RBC, Hb and PCV counts, this finding revealed that the plant may have a possible potential to inhibit erythropoietin release from the kidneys, which is the humoral regulator of RBC production and also affect the

oxygen-carrying capacity of the blood and the amount of oxygen delivered to the tissues since red blood cells and haemoglobin (Hb) are very important in transferring respiratory gases [108, 109]. The reduction might be due to the presence of saponin, which has been reported to reduce haematological parameters probably due to lysis of blood cells or suppression of blood synthesis [110]. This report is contrary to the findings from this present study, which demonstrated increase in blood levels of erythrocyte. The possible explanation to this observed difference might be the duration of the administration and dose administered. It is therefore possible that the excessive and long time consumption of *Vernonia amygdalina* by humans can lead to anaemic state.

Ofem, et al. [111] observed that extract *O. gratissimum* caused an increase in the erythrocyte count. This was confirmed by the increased haematocrit (PCV) and percentage Hb. In normal circumstances, local tissue anoxia apparently leads to the formation of a glycoprotein called erythropoietin, which stimulates increased production of erythrocytes [112]. It is very likely that *O. gratissimum* leaves extract contains erythropoietin-like agent(s) which is/are responsible for the increased production of erythrocytes. In Ofem's study, examination of the differential counts revealed that high doses of *O. gratissimum* led to reduction in lymphocyte count [111]. The reduction in lymphocyte count could probably be due to cell margination rather than destruction. It is also possible that the inflammation due to BPH stimulate the bone marrow to produce neutrophils and release them into the blood. Neutrophils are the major granulocytes to be activated when the body is invaded by bacteria and they provide the first line of defense against invading microorganisms [113]. The granules of the neutrophil contains many enzymes, which makes it a powerful and effective killer machine.

Obianime, et al. [114] reported that aqueous *O. gratissimum* leaf extract decreased PCV and Hb levels in the first week, whereas WBC and lymphocyte counts were increased during the first and second weeks, respectively, in male mice. This is contrary to our present study which demonstrated that *O. gratissimum* increased RBC, PCV and Hb. They attributed the reduced haematological effects of *O. gratissimum* to stimulation of adaptive mechanisms within the body against *O. gratissimum*-induced toxicity on the blood cells. They suggested that *O.*

gratissimum may have two different effects—oxidative or antioxidative—depending on the tissue/organ system under investigation and the duration of administration [114].

5. CONCLUSION

This study indicates that the three extracts have the potential to reverse the inflammation caused by BPH and also have the capacity to boost the numbers of red blood cells probably by inhibiting the hemolysis caused by inflammatory factors or by enhancing the production of red blood cell from the bone marrow. Indicating that the plants can lead to the formation of a glycoprotein called erythropoietin, which stimulates increased production of erythrocytes.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The Cross River University of Technology, Calabar, Nigeria, Animal Ethics Committee approved the study before the experiment and certified all experimental protocols.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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