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Histomorphological changes in induced benign prostatic hyperplasia with exogenous testosterone and estradiol in adult male rats treated with aqueous ethanol extract of *Secamone afzelii*

Mbaka Godwin [a,*], Anunobi Charles [b], Ogunsina Samson [c], Osiagwu Daniel [b]

[a] Department of Anatomy, Lagos State University College of Medicine, Ikeja, Lagos, Nigeria
[b] Department of Anatomic and Molecular Pathology, College of Medicine of the University of Lagos, Lagos, Nigeria
[c] Department of Anatomy, Olabisi Onabanjo University, Remo Campus, Ogun State, Nigeria

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ABSTRACT

Secamone afzelii (*S. afzelii*) used locally to manage benign prostatic hyperplasia (BPH) was used to treat exogenously induced BPH in adult male Wister rats. Male rats weighing 200 ± 10 g kg^{-1} had exogenous administration of testosterone and estradiol in staggered doses (three times weekly) for three weeks. The induced animals were in five groups (6 rats per group). Groups 1 and 2 received extract at 200 and 400 mg kg^{-1} body weight (bwt) by gavages for thirty days; group 3, finasteride (0.1 mg kg^{-1}); group 4, untreated for thirty days; group 5, negative control, which was sacrificed twenty-one days after induction. Group 6 received extract (400 mg kg^{-1}) and steroid hormones simultaneously; group 7, normal control. The extract caused marked decrease in prostate weight of BPH induced rats with the photomicrograph of the prostate showing extensive shrinkage of glandular tissue whereas glandular hyperplasia occurred in the negative control. Prostate specific antigen (PSA) level significantly ($p < 0.05$) decreased in the treated groups compared to negative control. Treatment with the extract/finasteride caused significant decrease in testosterone to a level comparable to normal. The BPH induced rats treated with *S. afzelii*/finasteride recorded marked increase in the levels of antioxidant enzymes compared to the negative control. *S. afzelii* effectively ameliorated prostatic hyperplasia exogenously induced by causing extensive shrinkage of glands and stroma. It also exhibited antioxidant properties and showed to be a good prophylaxis.

1. Introduction

The term benign prostatic hyperplasia (BPH) denotes non cancerous enlargement of prostate gland. It is more discretely defined as a non malignant enlargement of prostate gland characterized by proliferation of the cellular elements such as its epithelial and stromal cells into a discrete mass or nodules [1]. An enlarged prostate means the gland has grown bigger and as the gland grows, it can press on the urethra causing difficulty in urination. The discomfort presented by this condition during urination makes its occurrence worrisome. BPH is considered a normal part of the aging process in men which becomes apparent histological in about 40% of men in their fifties and nearly 90% of men in their eighties [2]. Although the actual cause of BPH remains incompletely understood, it is clear that androgens have a central role to play in its development [3]. Dihydrotestosterone (DHT), an androgen derived from testosterone through the action of 5α-reductase and its metabolite, 3α-androstanediol, seems to be the major hormonal stimuli for stromal and glandular proliferation in men with nodular hyperplasia. Experimental work has also identified age-related increases in estrogen levels that may increase the expression of DHT, the progenitor of BPH [4]. The incrimination of DTH in the pathogenesis of BPH forms the basis for the current use of 5α-reductase inhibitors in the treatment of symptomatic nodular hyperplasia.

The 5α-reductase inhibitors inhibit the development of BPH via a reduction in dihydrotestosterone (DHT) production [5]. Other therapeutic agents include α_1-adrenergic receptor antagonists considered more suitable for the management of BPH complication like lower urinary tract symptoms (LUTS) because they relax the smooth muscle in the prostate and the neck of the bladder [6,7]. These allopathic medications seem to trigger adverse effect like

* Corresponding author.
E-mail addresses: mbaakagm@yahoo.com (G. Mbaka), dozieanunobi@yahoo.com (C. Anunobi), Chiazuibe4@yahoo.com (S. Ogunsina), dosiagwu@unilag.edu.ng (D. Osiagwu).

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severe myopathy owing to their structural similarities to the steroid hormones [8]. There are also incidences of ejaculatory or erectile dysfunction and decreased libido associated with the use of these drugs [9].

The more worrisome aspect is that the treatment option requires that the drugs be used permanently because if they are suspended there would be reoccurrence of the symptoms [10].

Alternative therapy such as herbal medicine has been popular since the ancient time for the treatment of BPH [11]. Their popularity is based on the assumption that they are of natural source and therefore not harmful. More importantly is the fact that they are readily assessable, cheap and can be acquired without medical prescription. The phytotherapeutic agents used in the treatment of BPH could be recipes from a single plant source or could be extracts from two or more plant sources.

Secamone afzelii (*S. afzelii*) is a therapeutic agent that has wide application. It belongs to the family Asclepiadaceae and is widespread in West and Central Africa [12]. *S. afzelii* occurs in secondary forest and savanna thickets, it is also common in abandoned fields and field boundaries, growing in a wide range of climatic conditions particularly in the sun or in light shade [12]. Its medicinal value includes the use in the treatment of gonorrhea, cough and catarrh and as galactogogue [13]. Its leafy twig infusion is taken to treat sexually transmitted diseases, diabetes and schistosomiasis [14]. *S. afzelii* has been reported to show a high concentration of flavonoids, saponins, reducing sugars, coumarins and the triterpenoid friedelin [15]. Its leaf extract is used by traditional healers singly and in combination with other herbs to treat BPH with no known scientific proof. It is in this light that this study was designed to validate the claim.

2. Materials and methods

2.1. Plant materials

The aerial part of *S. afzelii* was collected from Ikenne-Remo, Ogun State, Nigeria. The plant sample was authenticated in the Forestry Research Institute of Nigeria (FRIN), Ibadan, where the voucher specimen was deposited in the herbarium (FHI/108940).

2.2. Preparation of aqueous ethanol extract of Sacamone afzelii

The aerial part of the plant was dried in the sun within the temperature range of 30–42 °C for 5 days before being subjected to size reduction to a coarse powder with electric grinder. The coarse powder of the plant weighing 780 g was extracted with 90% aqueous ethanol in three cycles using Soxhlet extractor. The crude extract was filtered with Whatman filter paper No. 4 and the filtrate concentrated *in vacuo* at 30 °C to obtain 68 g residue weight (8.7% w/w). The residue was stored in an air tight bottle kept in a refrigerator at 4 °C till used.

2.3. Animals

Adult male Wister rats (200 ± 5 g) obtained from the Animal House of the University of Ibadan, Oyo State, Nigeria, were kept under standard environmental condition of 12/12 h light/dark cycle. They were housed in polypropylene cages (6 animals per cage), and were maintained on mouse chow (Livestock Feeds Nigeria Ltd.) and provided with water *ad libitum*. They were allowed to acclimatize for 12 days to the laboratory conditions before the experiment. The use and care of the animals, and the experimental protocol were in strict compliance with the Institute of Laboratory Animals Research (ILAR) guidelines on the use and care of animals, in experimental studies [16].

2.4. BPH induction

Adult male rats weighing 200 ± 12 mg kg^{-1} were induced with BPH by exogenous administration of testosterone and estradiol in staggered doses (three times a week respectively) for three weeks. The steroid hormones were diluted with corn oil which served as the solvent. The preparation and induction of BPH was as described by Mbaka et al. [17].

2.5. Animal grouping and treatment

The induced animals were divided into five groups each comprised of 6 male rats. Groups 1 and 2 received the extract at 200 and 400 mg kg^{-1} body weight (bwt) by gavages for thirty days. Group 3 received finasteride at 0.1 mg kg^{-1}; group 4 was left untreated for thirty days before they were sacrificed to assess possible reversal of the exogenous induction; group 5 (negative control) was sacrificed immediately after the induction. Group 6 was given the extract (400 mg kg^{-1}) simultaneously as benign hyperplasia was being induced with the steroid hormones while group 7 served as normal control.

The animals were weighed prior to the commencement of the experiment and subsequently every five days till the end of the experiment. The prostate weight was equally recorded after the sacrifice.

2.6. Assay for testosterone and prostate specific antigen (PSA)

Enzyme immunoassay technique was used for the quantitative determination of testosterone concentration and PSA evaluation [18,19].

2.7. Oxidative activities

The oxidative activity assessment was conducted after overnight fast. The animals were sacrificed and the hepatic tissue harvested were homogenized and used for the assays.

2.7.1. Superoxide dismutase assay

Superoxide dismutase (SOD) was assayed utilizing the technique of Kakkar et al. [20]. A single unit of the enzyme was expressed as 50% inhibition of Nitroblue Tetrazolium (NBT) reduction/min/mg protein which was measured spectrophotometrically at 420 nm.

2.7.2. Catalase assay

Catalase (CAT) was assayed colourimetrically at 620 nm and expressed as μmoles of H_2O_2 consumed/min/mg protein [21]. The hepatic tissue was homogenized in isotonic buffer (pH 7.4). The homogenate was centrifuged at 1000 rpm for 10 min. The reaction mixture contained 1.0 mL of 0.01 M pH 7.0 phosphate buffers which was added 0.1 mL of tissue homogenate and 0.4 mL of 2.0 mL of dichromate-acetic acid reagent (5% potassium dichromate and glacial acetic acid mixed in 1:3 ratios).

2.7.3. Estimation of glutathione

The glutathione (GSH) level was determined by the method of Ellman [21]. To the hepatic homogenate was added 10% trichloroacetic acid (TCA) and centrifuged. 10 mL of the supernatant was treated with 0.5 mL of Ellmans' reagent in 100 mL of 0.1% of sodium nitrate and 3.0 mL of phosphate buffer (0.2 M, pH 8.0). The absorbance was read at 412 nm.

2.7.4. Estimation of lipid peroxidation

Lipid peroxidation as evidenced by the formation of thiobarbituric acid reactive substances (TBARS) and hydroperoxides (HP)

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