

Ameliorating Effects of *Annona Muricata* Leaf Extract on Hormonal Profile in Male Wistar Rats

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ABSTRACT

A total of 78 adult male rats obtained from the laboratory animal production unit of the Department of Physiology, Abia State University, Uturu were used for the different segments of the study. Eighteen of the rats were used for acute toxicity/lethal dose evaluation of the extract while the remaining sixty (60) were used for the testosterone-induced hyperplasia study. Prostate hyperplasia was induced in the rats via daily sub-cutaneous administration of testosterone propionate (5 mg/kg body weight) for 28 days. Sixty rats used for this segment of the study were assigned to 6 groups of 10 rats and treated as follows: Group 1, Normal control, no treatment. Group 2 Testosterone propionate (5 mg/kg) only and was the BPH control. Group 3, Testosterone propionate (5 mg/kg bw) + Finasteride (3 mg/kg body weight). Group 4, Testosterone propionate (5 mg/kg bw) + *Annona Muricata* Leaf extract (300 mg/kg body weight). Group 5, Testosterone propionate (5 mg/kg bw) + *Annona Muricata* Leaf extract (600 mg/kg body weight). Group 6, *Annona Muricata* Leaf extract (600 mg/kg bw) only. At the end of treatment with *Annona muricata* (soursop) extract, animals were sacrificed and blood samples were collected into EDTA and plain bottles and then centrifuged at 3000 rpm for 10 minutes to obtain clear sera samples which were used for hormonal assayed. Data obtained were subjected to Statistical Package for Social Sciences (SPSS, Version 20.0, IBM SPSS Inc, Chicago, IL) was used for data analysis. Level of significance was calculated by One Way Analysis of Variance (ANOVA). Data were analyzed using Duncan Multiple Range Test and complemented with Student's *t* test for post-hoc test for comparisons of the means of the various doses and fractions. *P*- values less than 0.05 were considered statistically significantly different between the test and control groups as well as among test groups for measured value. Conclusively, *Annona muricata* leaf extract showed modulatory effects on hormonal profile levels, including testosterone, which are pivotal in male reproductive health.

Keywords: *Annona muricata* leaf extract, testosterone-induced hyperplasia, modulatory effects, hormonal profile and wistar rats

INTRODUCTION

The hormonal regulation of the reproductive system involves a complex interplay between various hormones, primarily testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). *Annona muricata* (soursop), known for its diverse medicinal properties, has been the focus of numerous studies investigating its potential effects on these crucial reproductive hormones.[3,8] Testosterone is the principal male sex hormone responsible for the development of male reproductive tissues and secondary sexual characteristics. It also plays a vital role in spermatogenesis, libido, and overall male fertility.[12] The impact of *Annona muricata* on testosterone levels has been explored in several studies. According to Eyeghre *et al.* (2023), extracts of *Annona muricata* showed significant modulation of testosterone levels in animal models, suggesting its potential role in supporting reproductive health.[7]

Follicle-stimulating hormone (FSH) is essential for the regulation of spermatogenesis in males. FSH stimulates the Sertoli cells in the tests, which in turn support the maturation of sperm cells. Any alteration in FSH levels can significantly impact sperm production and male fertility.[14] Research by Arhoghro *et al.* (2023) indicates that *Annona muricata* may influence the levels of FSH, potentially enhancing its activity and thus improving spermatogenesis.[3]

Because it stimulates the Leydig cells in the testes, luteinizing hormone (LH) is essential for controlling the generation of testosterone. LH secretion is crucial for maintaining adequate levels of testosterone, which is necessary for the proper functioning of the male reproductive system.[10] Studies have

demonstrated that *Annona muricata* extracts can affect LH levels. For instance, a study by Arhoghro *et al.* (2023) showed that the administration of *Annona muricata* extract resulted in significant changes in LH levels, which could influence overall testosterone synthesis and reproductive health.[3]

The mechanisms through which *Annona muricata* exerts its effects on these hormones are not entirely understood, but several hypotheses have been proposed. One potential mechanism involves the plant's antioxidant properties. Oxidative stress is known to negatively impact hormonal balance and reproductive function. *Annona muricata* contains high levels of antioxidants, such as flavonoids and acetogenins, which can mitigate oxidative stress and improve hormonal regulation.[13]

MATERIALS AND METHODS

Equipment's used include sensitive weighing balance, Electric weighing balance, Manual blender, Dissecting set, Dissecting board, 5ml syringes, 1ml syringes, test tubes, serum bottles, Sample bottles, EDTA bottles, whatman No 1 filter paper, Measuring cylinders, Pasteur pipette, Cotton wool, Micro pipette, Rat cages, Feeding and water trough, Oral gavage, Glass column, Microscope, Glass TLC plates, microscope slides, Glass wool, funnel, Spatula, Retort stand, Hand gloves, TLC tank, beaker, Oven, freezer, Refrigerator, Spectrophotometer(722N, Mindray, MC Quijing, China), Centrifuge, Rotary evaporator, Soxhlet extractor, GC-MS machine, Chemoilluminoscene machine and Haematology analyser (BC-2300, Mindray, MC Quijing, China).

ETHICAL APPROVAL

This study was approved by the research and ethical committee of the Department of Physiology, Abia State University, Uturu.

Animals

A total of 78 adult male rats obtained from the laboratory animal production unit of the Department of Biochemistry, Abia State University, Uturu were used for the different segments of the study. Eighteen of the rats were used for acute toxicity/lethal dose evaluation of the extract while the remaining sixty (60) were used for the testosterone-induced hyperplasia study. The animals were housed in aluminum cages, under standard conditions 12/12h light-dark cycle at temperatures of $25\pm 2^{\circ}\text{C}$ and were fed with standard grower pellets (Grand Cereals Ltd, Abia State) and had access to clean drinking water for seven days of acclimatization before the initiation of experiment. All experiments were carried out in accordance with International Guideline for Biomedical Research (CIOMS/OMS, 1985) and as approved by the Department of Physiology, Abia State University, Uturu.

Experimental Design for the Hyperplasia Study

Prostate hyperplasia was induced in the rats via daily sub-cutaneous administration of testosterone propionate (5 mg/kg body weight) for 28 days. Sixty rats used for this segment of the study were assigned to 6 groups of 10 rats and treated as follows:

- Group 1 - Normal control, no treatment
- Group 2 - Testosterone propionate (5 mg/kg) only and was the BPH control
- Group 3 - Testosterone propionate (5 mg/kg bw) + Finasteride (3 mg/kg bw)
- Group 4 - Testosterone propionate (5 mg/kg bw) + AML extract (300 mg/kg bw)

- Group 5 - Testosterone propionate (5 mg/kg bw) + AML extract (600 mg/kg bw)
- Group 6 - AML extract (600 mg/kg bw) only

At the end of treatment, animals were sacrificed, and blood samples were collected into EDTA and plain bottles and then centrifuged at 3000 rpm for 10 minutes to obtain clear sera samples which were used for hormonal assayed

Preparation of Plant Extracts

Plant extracts were prepared in accordance with the method used by Orieke *et al.*, (2019). The freshly collected leaves of *Anona muricata* were air dried under shade within 14 days and were thereafter pulverized into coarse powdered form using a locally fabricated grinding machine. Two solvents, ethanol and N-hexene were used for the preparation of the extracts. A known quantity (300g) of the powdered plant material was macerated in 1.5 litres of ethanol (AR) for 48 hours, been shaken violently every two hours during that time. The filtrate, which was the extract in solution, was then obtained by filtering it through Whatman No. 1 filter paper.

The filtrate so obtained was concentrated at low temperature to obtain a solid dark-green extract which weighed 13.91 g and represented 4.64% extract yield. The extract was preserved in the refrigerator at -4°C until needed and is hereafter referred to as *Anona muricata* leaf (AML) extract.

Determination of Serum Reproductive Hormone Levels

The hormones assayed were testosterone, Follicle Stimulating Hormone and luteinising hormone, in accordance with standard procedures outlined by the kits producer AUTOBIO DIAGNOSTICS CO., LTD. Zhengzhou, China (Dabhadkar *et al.*, 2013).

**Luteinizing Hormone (LH)
Chemiluminescence Immunoassay Kit.
Catalog No. CL1101-2**

Materials provided

Antibody Coated Microtiter Plate. Microplate with anti-LH monoclonal antibody (MAb) coated wells (1 plate, 48wells/96 wells). Enzyme Conjugate Reagent. Horseradish peroxidase (HRP) labeled anti-LH (MAb) in Stabilizing Buffer (1 vial, 3.0 ml/6.0ml). Reference Standards: 1.0, 2.5, 10, 40, 160mIU/m. (5 vials, Lyophilized). Substrate A: (1 vial, 3.5ml/6.0ml). Substrate B: (1 vial, 3.5ml/6.0ml). PBS-T powder: PBS-Tween (1bag, 5g). Precision pipettes and tips: 0.05ml, 0.1ml, 1.0ml. Distilled water. Vortex mixer. Absorbent paper or paper towel. Graph paper. Luminometer.

Principle

A solid phase two-site immunoassay is the LH CLIA test. The microtiter wells are coated with one monoclonal antibody, and the tracer is another monoclonal antibody that has been labeled with horseradish peroxidase. The two antibodies are "sandwiched" between the LH molecules found in the serum or standard solution. Following the formation of the coated antibody-antigen-antibody-enzyme complex, the unbound antibody-enzyme labels are removed by washing. The horseradish peroxidase activity bound in the wells is then assayed by chemiluminescence reactions. The related light unit (RLU) of the reaction is proportional to the concentration of LH present in the sample.

Procedure

Secure desired number of coated wells in a holder and dispense 50µl of LH standards, specimens, and controls into appropriate wells. Fill each well with 50µl of the Enzyme Conjugate Reagent and stir gently for 30 seconds. At 37°C, incubate for 60 minutes. Empty the plate contents into a

rubbish receptacle to remove the mixture at the conclusion of the incubation. Rinse the microtiter plate 5 times with washing buffer and stroke sharply on an absorbent paper or paper towels to remove all residual water droplets. Thereafter, dispense 50µl of substrate A and 50µl of substrate B reagent into each well and gently mix for 10 seconds and incubated at room temperature in the dark for 5 minutes without shaking. Finally read the RLU values with a Luminometer.

**Follicle Stimulating Hormone (FSH)
Chemiluminescence Immunoassay Kit.
Catalog No. CL1102-2**

Materials provided

Antibody Coated Microtiter Plate: Microplate coated with monoclonal antibodies to Follicle-Stimulating Hormone (anti-FSH MAb) (1 plate, 48 wells/96wells); Enzyme Conjugate Reagent: Horseradish peroxidase (HRP) labeled anti-FSH MAb in Stabilizing Buffer (1 vial, 6.0ml/11.0ml); Reference Standards: 1, 2.5, 10, 40 and 160mIU/ml FSH in Stabilizing Buffer (5 vials, 0.5ml/ea); Substrate A (1 vial, 3.5ml/6.0ml); Substrate B (1 vial, 3.5ml/6.0ml) 6. PBS-T powder: PBS-Tween (1bag, 5g); Precision pipettes and tips, 0.025ml, 0.1ml, 1.0ml; Distilled water; Vortex mixer; Absorbent paper or paper towel; Graph paper; Luminometer.

Principle

A solid phase two-site immunoassay is the FSH CLIA test. The microtiter wells are coated with one monoclonal antibody, and the tracer is another monoclonal antibody that has been labeled with horseradish peroxidase. The two antibodies are "sandwiched" between the FSH molecules found in the serum or standard solution. The unbound antibody-enzyme labels are eliminated by washing after the coated antibody-antigen-antibody-enzyme complex has formed. The horseradish peroxidase activity bound in the wells is

then assayed by chemiluminescence reactions. The related light unit (RLU) of the reaction is proportional to the concentration of FSH present in the sample.

Procedure

25µl of FSH standards, specimens, and controls should be dispensed into the appropriate wells in a holder's coated wells in the correct number. Pour 100 µl of the Enzyme Conjugate Reagent into each well, then stir gently for 30 seconds. The mixture should be incubated at 37°C for 60 minutes. Empty the plate contents into a rubbish receptacle to remove the mixture at the conclusion of the incubation. Rinse the plate five times with washing buffer after emptying the microtiter. To get rid of any remaining water droplets, swat the microtiter plate firmly into paper towels or absorbent paper. Next, fill each well with 50 µl of the substrate A and 50 µl of the substrate B reagents, and stir gently for 10 seconds. Use a Luminometer to measure the RLU readings after the mixture has been incubated for five minutes at room temperature without shaking in the dark.

Testosterone Chemiluminescence Immunoassay Kit Catalog No. CL1104-2

Materials

Antibody Coated Microtiter Plate: Goat anti-mouse IgG-coated microplate (48/96 wells). Anti-Test Reagent: Mouse monoclonal antibodies to Test (anti-Test MAb) in Stabilizing Buffer (1 vial, 3.0ml/6.0ml); Enzyme Conjugate Reagent: Horseradish peroxidase (HRP) labeled testosterone (Test) in Stabilizing Buffer (1 vial, 3.0ml/6.0ml). PBS-T Powder: PBS-Tween (1bag, 5g); Precision pipettes and tips, 0.025ml, 0.05ml; Reference Standards: 0, 0.5, 1, 2.5, 10, and 20 ng/ml (6 vials, 0.5ml/ea); Substrate A: 1 vial, 1.8ml/3.5ml; Substrate B: 1 vial, 1.8ml/3.5ml. water that has been distilled.

a vortex mixer. paper towels or absorbent paper. graph paper. Luminometer.

Principle

In the Test CLIA test procedure, the testosterone standard or patient serum is incubated with the testosterone antibody and the testosterone-horseradish peroxidase conjugate in the anti-mouse IgG coated well. The antibody-bound testosterone in this solid-phase system will stay on the well, whereas the unbound testosterone will be washed off. When the antibody-bound testosterone-horseradish peroxidase enzyme combination is combined with the CLIA substrate, a chemiluminescence reaction is produced. The quantity of unlabeled test in the sample has an inverse relationship with the Related Light Unit (RLU), which is proportional to the amount of enzyme present. The concentration of the test in the unidentified sample is measured in relation to a set of test standards that are tested in the same manner.

Procedure

In the desired number of coated wells placed in a holder add 25µl of Reference Standards, specimens, and controls into appropriate wells. Dispense 50µl of Anti-Test Reagent and 50µl of Enzyme Conjugate Reagent into each well and mix gently for 30 seconds. Incubate the mixture at room temperature for 60 minutes. Remove the incubation mixture by emptying the plate content into a waste container and then rinse the microtiter plate 5 times with washing buffer. Strike the microtiter plate sharply onto absorbent paper or paper towels to remove all residual water droplets. Add 25µl of substrate A and 25µl of substrate B into each well. Mix gently for 10 seconds. Incubate the mixture at room temperature in the dark for 10 minutes without shaking, thereafter reading the RLU values with a Luminometer.

DATA ANALYSIS

Statistical Package for Social Sciences (SPSS, Version 20.0, IBM SPSS Inc, Chicago, IL) was used for data analysis. Level of significance was calculated by One Way Analysis of Variance (ANOVA). Data was analyzed using Duncan Multiple Range Test and complemented with

Student's t test for post-hoc test for comparisons of the means of the various doses and fractions. P- values less than 0.05 were considered statistically significantly different between the test and control groups as well as among test groups for measured value.

RESULTS

Table 1: Hormonal Profile levels.

Treatments	Normal control	BPH control (Testosterone only)	Finasteride (3 mg/kg) + Testosterone	AML extract (200 mg/kg) + Testosterone	AML extract (400 mg/kg) + Testosterone	AML extract (800 mg/kg) + Testosterone
PSA (ng/ml)	0.15±0.05 ^a	3.05±0.16 ^c	1.43±0.41 ^b	1.22±0.18 ^b	1.38±0.17 ^b	0.11±0.02 ^a
Testosterone (ng/ml)	12.91±0.86 ^a	15.88±0.94 ^b	12.51±0.34 ^a	13.06±0.56 ^a	12.32±0.26 ^a	12.05±0.81 ^a
FSH (miu/ml)	7.22±0.13 ^c	5.33±0.49 ^a	6.21±0.23 ^b	6.39±0.41 ^b	6.68±0.28 ^{b,c}	7.15±0.18 ^c
LH (miu/ml)	5.64±0.12 ^{a,b}	6.25±0.03 ^d	5.93±0.14 ^c	5.69±0.23 ^{a,b,c}	5.80±0.13 ^{b,c}	5.51±0.09 ^a

Values are presented as mean ± standard deviation (n = 3); and means with different letter superscripts are significantly (P < 0.05) different from paired mean across the row.

Table 1, presents the results of hormonal levels across different treatment groups, indicating significant variations compared to the normal control. The BPH control (Testosterone only) group shows markedly elevated levels of prostate-specific antigen (PSA) (3.05±0.16 ng/ml), indicating prostate enlargement. Testosterone levels are also elevated (15.88±0.94 ng/ml) compared to the normal control (12.91±0.86 ng/ml). Treatment with

Finasteride (3 mg/kg) + Testosterone reduces PSA levels (1.43±0.41 ng/ml) closer to normal values and maintains testosterone levels (12.51±0.34 ng/ml). The groups treated with AML extract (200 mg/kg, 400 mg/kg, and 800 mg/kg) + Testosterone show varying effects on PSA and testosterone levels, generally reducing PSA to near-normal levels and maintaining testosterone within a normal range. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels also show variations across groups, with some treatments demonstrating modulation towards normal levels.

DISCUSSION

The hormonal analysis highlights significant variations in hormone levels across different treatment groups, reflecting the effects of *Annona muricata* leaf (AML) extract in the context of benign prostatic hyperplasia (BPH) induced by testosterone, as discussed in relevant literature.[1,7] In the BPH control group (Testosterone only), prostate-specific antigen (PSA) levels were markedly elevated (3.05 ± 0.16 ng/ml), indicating prostate enlargement, which is consistent with testosterone-induced BPH.[4,5] Testosterone levels were also elevated (15.88 ± 0.94 ng/ml) compared to the normal control (12.91 ± 0.86 ng/ml), further confirming the induction of BPH. Treatment with Finasteride (3 mg/kg) + Testosterone effectively reduced PSA levels (1.43 ± 0.41 ng/ml) towards normal values, demonstrating its role in mitigating prostate enlargement by inhibiting dihydrotestosterone synthesis.[2,15] Testosterone levels in this group (12.51 ± 0.34 ng/ml) were maintained within the normal range, indicating a regulatory effect of Finasteride on hormone balance. Groups treated with AML extract (200 mg/kg, 400 mg/kg, and 800 mg/kg) + Testosterone showed varying effects on PSA and testosterone levels. Generally, AML extract treatments reduced PSA levels to near-normal values and helped maintain testosterone within the normal range, suggesting potential anti-hyperplastic effects.[6,11] This aligns with findings indicating AML's modulation of hormonal imbalances associated with BPH, possibly through its phytochemical constituents such as acetogenins and flavonoids.[9] Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels also exhibited

variations across treatment groups, with some treatments showing modulation towards normal levels. This indicates a broader regulatory effect of AML extract on endocrine function, potentially supporting overall hormonal balance in BPH conditions.

CONCLUSION

Conclusively, *Annona muricata* leaf extract showed modulatory effects on hormonal profile levels, including testosterone, which are pivotal in male reproductive health.

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