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Citrullus lanatus Rind and Juice Extracts as Probable Therapeutics in the Prevention and Management of Induced Benign Prostatic Hyperplasia

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Authors' contributions

This work was carried out in collaboration between both authors. Author RSA designed the study, supervised the experiment, wrote the protocol, formed the statistical analysis and wrote the final draft of the manuscript. Authors RSA and OLO did the literature searches. Author OLO performed the experiment and managed the results. Both authors read and approved the final manuscript.

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ABSTRACT

Introduction: Benign prostatic hyperplasia (BPH) afflicts about 90% of men in the 9th decade of life. Its management could pose socio-economic challenges. *Citrullus lanatus* is widely cultivated and known to have antioxidant properties that could impact positively on the management of BPH.
Aim: The ameliorative effect of the rind and juice of *Citrullus lanatus* in induced BPH in Wistar rats was investigated.
Methodology: Forty adult male Wistar rats in eight equal groups were used for the experiment. The normal control group was NC while the BPH induced but untreated group was CI. The aqueous rind concomitant (ARC) and ethanolic rind concomitant (ERC) groups had administration of the respective extract of the rind simultaneously with the induction of BPH. The aqueous rind

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post-induction (ARP), ethanolic rind post-induction (ERP) and juice post- induction (JP) groups had respective extract after induction of BPH. The last group was juice concomitant (JC). Upon conclusion of the study, the animals were ethically sacrificed; the prostate glands harvested for measurement, histological analysis and oxidative stress evaluation {superoxide dismutase (SOD), catalase (CAT), gluthatione peroxidase (GPx) and malondialdehyde (MDA)}.

Results: The CI group had significantly higher mean prostate weight than groups NC, ARP and ERP (*P< 0.05*). The respective activities of SOD, CAT and GPx in ARC, ERC, JC, ARP, ERP and JP were significantly (*P< 0.05)* higher than in CI. The MDA concentrations were significantly (*P< 0.05)* lower in ARC, ERP and JP than CI.

Histology of the JC prostate gland showed non-hyperplasia.

Conclusion: The study showed that the rind and juice of *Citrullus lanatus* reduced the enlarged prostate gland, ameliorated the associated oxidative stress and restored the altered picture of the prostate in induced BPH. Thus *Citrullus lanatus* may be of medicinal relevance in the prevention and management of BPH.

Keywords: Benign prostatic hyperplasia; Citrullus lanatus rind and juice; oxidative stress.

1. INTRODUCTION

Benign prostatic hyperplasia (BPH) is an enlargement of the prostate gland characterized by overgrowth of the transitional and periurethral zones due to stromal and glandular proliferation. It is part of the ageing process in men and about 90% of them in the 9th decade of life are afflicted [1,2]. Though it is not a cancer, its clinical presentation is usually with distressing symptoms and signs and its management is of considerable financial and emotional burden.

Non-surgical management of human diseases entails chemotherapeutic agents (synthetic or natural) and medicinal plants. Various plant parts are in use by mankind for the management of diverse ailments. The ability of high doses of the seeds and oil of pumpkin at shrinking the prostate gland in induced BPH in rats is well documented [3-5]. Plants, being natural have the likelihood of lesser toxicity than the synthetic drugs. This is being taken advantage of in pharmacognosy. As a result of intensive and diverse studies in plant chemistry, the efficacy of chemotherapeutic agents is being improved upon on continuous basis [6].

Citrullus lanatus (watermelon) is a vine-like flowering plant of the Cucurbitaceae family originally from Southern Africa. Its fruit has a thick outer portion known as the rind (exocarp) and a fleshy centre that consists of the mesocarp and endocarp. The latter portion is 91% water and 6% sugar content [7-9]. The root has been described to be emetogenic and a purger [10]. Also the extracts of the fruit and seed of the plant have been demonstrated to exhibit broad spectrum antimicrobial activity [11]. The medicinal properties of *C. lanatus* seed have been extensively studied. Such attributes of the seed in rats include antimicrobial, anti-inflammatory, antioxidant and analgesia [11,12]. Extract of the fleshy portion of *C. lanatus* has been reported to be hypoglycemic in rats with induced diabetes mellitus and also as a laxative [13,14]. The ability to reduce gastric acid secretion and promote ulcer healing in rats with induced gastric ulceration has been ascribed to both the juice and seed of the plant [15,16].

The rind is usually light green (some may be dark green) with few longitudinal white stripes. It is the fleshy portion that is usually consumed while the rind, though edible is usually discarded as waste. Studies that have documented the beneficial effects of the commonly edible portion on experimentally induced BPH in laboratory animals are available but those of the rind are not [17-19]. From the foregoing, the need to explore the rind as a possible preventive and or therapeutic agent in the management of BPH is important, hence the justification for this study.

2. MATERIALS AND METHODS

2.1 Plant Materials

2.1.1 Collection and identification of plant materials

Fresh water melon fruits were procured from a grocery outlet in Bodija market, Ibadan, Nigeria. Authentication was at Forestry Research Institute of Nigeria (FRIN), Ibadan and voucher specimen (FHI. 110098) was deposited at the FRIN herbarium.

2.1.2 Preparation of extracts

After cleansing of the fruits with distilled water, the rinds were peeled off and dried at room temperature with filtered air. The dried rinds were initially minced with sharp knife and subsequently blended by means of a grinder to produce very fine powdery substance that was used for extraction. The ethanolic extract was obtained by mixing ten grammes (10 g) of the *Citrullus lanatus* powder with 100 mls of 70% ethanol using the method described by Panovska [20]. A 12% yield was obtained and this was used for the experiment. Ten grammes of the powder was also used to prepare the aqueous extract of the rind and a10% yield was obtained. By sequential homogenization, centrifugation and filtration; the juice was obtained from the fleshy portion of *C. lanatus.*

2.2 Animals

Forty adult male Wistar rats with a weight range of 145 to 220 g were sourced from the animal house of the College of Medicine, University of Ibadan. They were acclimatized for two weeks in a well ventilated and illuminated environment with optimal ambient temperature (27±3℃, 12 hours light / dark cycle) that was conducive for the study. The animals were fed liberally with locally sourced but standard pelletized rat feed and had unrestricted water intake.

2.3 Design of the Experiment

The criteria for animal grouping were the interventional agent and the timing of its administration. Thus the concomitant groups had the interventional agent administered simultaneously with the induction of BPH while those of the post- induction groups had it after induction of BPH. Sequel to these criteria, the 40 rats were randomly allotted into eight equal groups. The details of these groups were as stated below;

(1). Normal Control (NC) –not induced
(2). Induced Control (CI) – induced but untreated
(3). Aqueous Rind Concomitant (ARC)
(4). Ethanolic Rind Concomitant (ERC)
(5). Juice Concomitant (JC)
(6). Aqueous Rind Post- induction (ARP)
(7). Ethanolic Rind Post- induction (ERP)
(8). Juice Post- induction (JP)

2.4 Benign Prostatic Hyperplasia Induction

Testosterone (Green Field Pharm. JIANG SU Ltd, China) and oestradiol (Medipharm Pvt. Lahore, Pakistan) were administered for the induction of benign prostatic hyperplasia. Goya oil was used as diluent for the hormones. The hormones were administered subcutaeously at the inguinal region with oestradiol at 800 µg and testosterone at 3,000 µg /kg body weight every other day for three weeks [18-21].

2.5 Conduct of the Experiments

Prior to the commencement of the experiment, a pilot study was conducted to establish the ability of the induction of BPH by the methodology stated in section 2.4. The result of this pilot study histologically confirmed BPH.

All the post induction groups, (ARP, ERP and JP) had oral administration of respective extract at 250 mg/kg body weight daily for three weeks.

For the groups ARC, ERC and JC (concomitant groups), the respective oral extract was administered concomitantly with the hormones.

The two control groups (NC and CI) had water and rat feed for same duration.

The rats were weighed at the commencement and expiration of the experiment and average values for each group were noted and documented.

After three weeks of intervention, the animals were humanly euthanized under sedation with parenteral ketamine hydrochloride and diazepam. The prostate gland of each animal was harvested, weighed and subsequently sectioned into equal halves with a portion processed for light microscopy using Hematoxylin and Eosin (H & E) stain and the other fraction for oxidative stress analysis [Superoxide dismutase (SOD); Catalase (CAT); Gluthatione peroxidase (GPx) and Malondialdehyde (MDA)].

2.5.1 Oxidative stress analysis

The harvested prostate glands used for the assay of the antioxidants and prooxidant were preserved in phosphate buffer solution, subsequently homogenized and thereafter, cold

centrifuged at 12,000 rpm to obtain the supernatants which were used for the assays.

(a) Superoxide dismutase (SOD) assay- this was done using the autooxidation of pyrogallol absorbance spectrophotometry technique as described by Mccord and Fridovich [22].
(b) Catalase assay was by the method described by Aebi [23] using spectrophotometry of the erythrocyte lysate solution.
(c) Glutathione peroxide (GPx) assay was by spectrophotometric analysis of the enzymatic reaction to glutathione using the method described by Rotruck [24].
(d) Malondialhyde assay was by estimation of MDA reactive products using thiobarbituric acid as described by Ohkawa [25].

2.6 Data Analysis and Processing

The numerical parts of the results were analyzed with Statistical Package for the Social Sciences (SPSS) version 20 and expressed as percentages and means plus / minus standard deviation of means (±SD). Comparisons between groups were performed with one way analysis of variance (ANOVA) using the Post hoc Least Significance Difference (LSD) test and the level of significance was set at *p<0.05.*

3. RESULTS

3.1 Body Weight

All the groups had increased body weights with the CI group having the least percentage body weight change and that of ARP being the highest (Table 1).

3.2 Prostate Parameters

The smallest mean weight of the prostate was from NC while the largest value was that of group ARC. The distribution of the ratio of the mean prostate weight to the mean body weight of the animals followed similar pattern (Table 2).

3.3 Oxidative Stress Parameters

The activities of all the antioxidants namely superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) were significantly higher in all the experimental groups

Table 1. Mean group weight and weight change

Group	Initial mean body weight (g)	Final mean body weight (g)	Mean body weight change (g)	Body weight change (%)
NC	170±15.81	193±17.54	23±2.74	13.5
CI	186±8.94	191±8.22	5±9.35	2.7^{a**}
ARC	172.50±25.25	184±18.17	11.50±18.84	6.7^{a*}
ERC	177.50±14.79	192.50±8.29	15±8.66	8.5^{a*}
JC	176±18.51	185±18.71	9±7.42	5.1^{a**}
ARP	155±27.39	187±12.04	32 ±20.46	20.6^{b*}
ERP	144±19.81	160±21.51	16±22.19	11.1
JP	147±15.25	170±7.07	23±20.80	15.6

The mean body weight change of NC was significantly higher than that of (a) CI, ARC, ERC and JC, while that of CI was significantly lower than (b) ARP. $^{*}P< 0.05$ and $^{**}P< 0.01$

Table 2. Mean parameters of the prostate gland

Group	Prostate weight (g)	Prostate body weight ratio (10^{-3})
NC	$0.18±0.42^{a**}$	$0.92±0.24^{b**}$
CI	0.37±0.10	1.94±0.48
ARC	0.43±0.08	2.30 ±0.33
ERC	0.39±0.08	2.02 ±0.37
JC	0.30±0.07	1.64 ±0.38
ARP	$0.23±0.05^{a*}$	$1.23±0.18^{b*}$
ERP	$0.24±0.06^{a*}$	$1.49±0.20^{b*}$
JP	0.39±0.07	2.30±0.45

The group CI had significantly higher mean prostate weight than groups NC, ARP and ERP (a), while the ratio of the mean body weight to the prostate weight of groups NC, ARP and ERP were significantly lower than that of CI (b). $^{*}P< 0.05$ and $^{**}P< 0.01$

than the CI but significantly lower in comparison to NC group. The malondialdehyde (MDA) concentrations were lower in all the experimental groups (except ERC) than in the group CI but were all higher than that of group NC (*P< 0.05, **P< 0.01and ***P< 0.001) (Table 3).

3.4 Light Microscopy (Histology) of the Prostate Gland

Sections obtained from the normal control group (NC) showed scanty stroma with thin single-layered epithelium while those of the induced but untreated group (CI) exhibited crowded stroma with hyperplasic glandular elements (Plate 1). Similar features were seen in most of the experimental groups except for the JC group whose features were akin to that of group NC (Plates 2 & 3).

4. DISCUSSION

All the groups had increased mean body weight change to a variable extent with the induced but untreated group (CI) having the least while the group APP had the highest value. This might be

Table 3. Mean activities of oxidative stress indicators

Group	SOD (µmol/mg)	CAT (µmol/mg)	GPx (µmol/mg)	MDA (µmol/mg)
NC	$1.22\pm0.13^{a**}$	$5.98\pm1.06^{b**}$	$1.61\pm0.02^{c***}$	$0.89\pm0.05^{d**}$
CI	0.60±0.03	1.51±0.56	0.87±0.04	1.99±0.16
ARC	$1.15\pm0.10^{a*}$	$4.95\pm2.47^{b*}$	$1.12\pm0.11^{c*}$	$1.36\pm0.07^{d**}$
ERC	$0.83\pm0.23^{a**}$	$4.36\pm0.59^{b*}$	0.97±0.09	2.04±0.32
JC	$0.70\pm0.10^{a***}$	$4.92\pm1.02^{b*}$	$1.07\pm0.17^{c*}$	1.73±0.13
ARP	$0.76\pm0.04^{a**}$	1.99±0.30	$1.42\pm0.25^{c*}$	1.47±0.15
ERP	$0.94\pm0.20^{a**}$	$4.44\pm1.61^{b*}$	$1.33\pm0.18^{c**}$	$1.15\pm0.20^{d**}$
JP	0.95±0.24	$4.22\pm0.54^{b*}$	$1.46\pm0.40^{c**}$	$1.61\pm0.11^{d*}$

The respective activity of SOD, CAT and GPx for the CI group was significantly lower than that of NC (a, b & c).However, the MDA activity of CI was significantly higher than that of group NC (d).
*The SOD activities of groups ARC, ERC, JC, ARP and ERP were significantly higher than that of the group CI (a). For the CAT activities, groups ARC, ERC, JC, ERP and JP, were significantly elevated above that of group CI (b). Groups ARC, JC, ARP, ERP and JP had significantly higher activities of GPx than group CI (c). The MDA concentrations of ARC, ERP and JP were significantly lower than that of CI (d). *P< 0.05, **P< 0.01and ***P< 0.001*

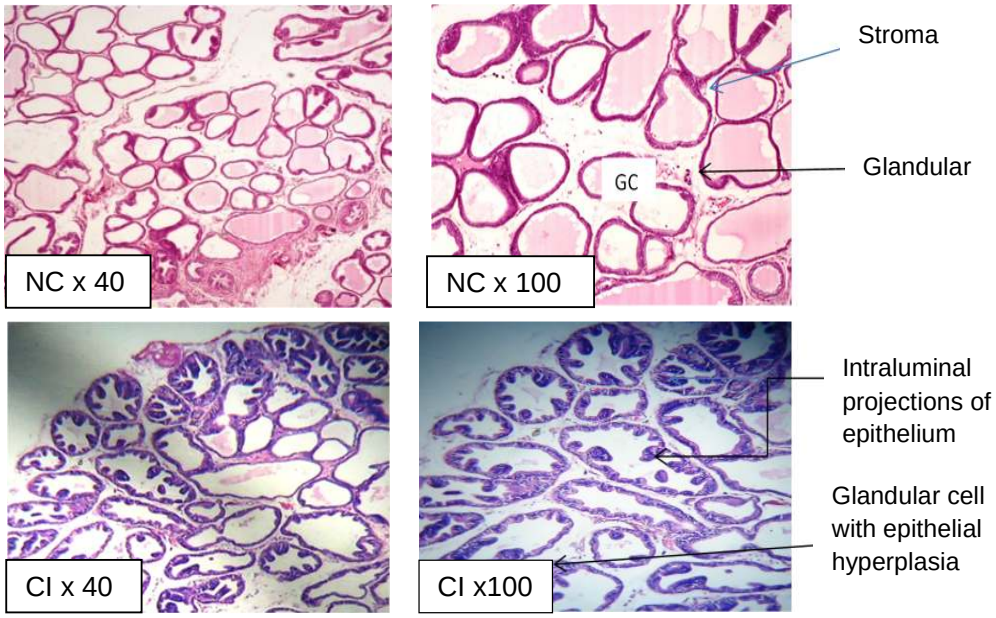

Plate 1. Prostate gland of the control groups (H & E)
The slides prepared from the specimen of the Normal Control (NC) group showed normal stromal and glandular pattern consistent with normal prostate gland in the rat. However, the epithelium of the Induced Control (CI) group showed increased cellularity projecting into the lumen, these features were those of enlarged prostate gland (BPH)

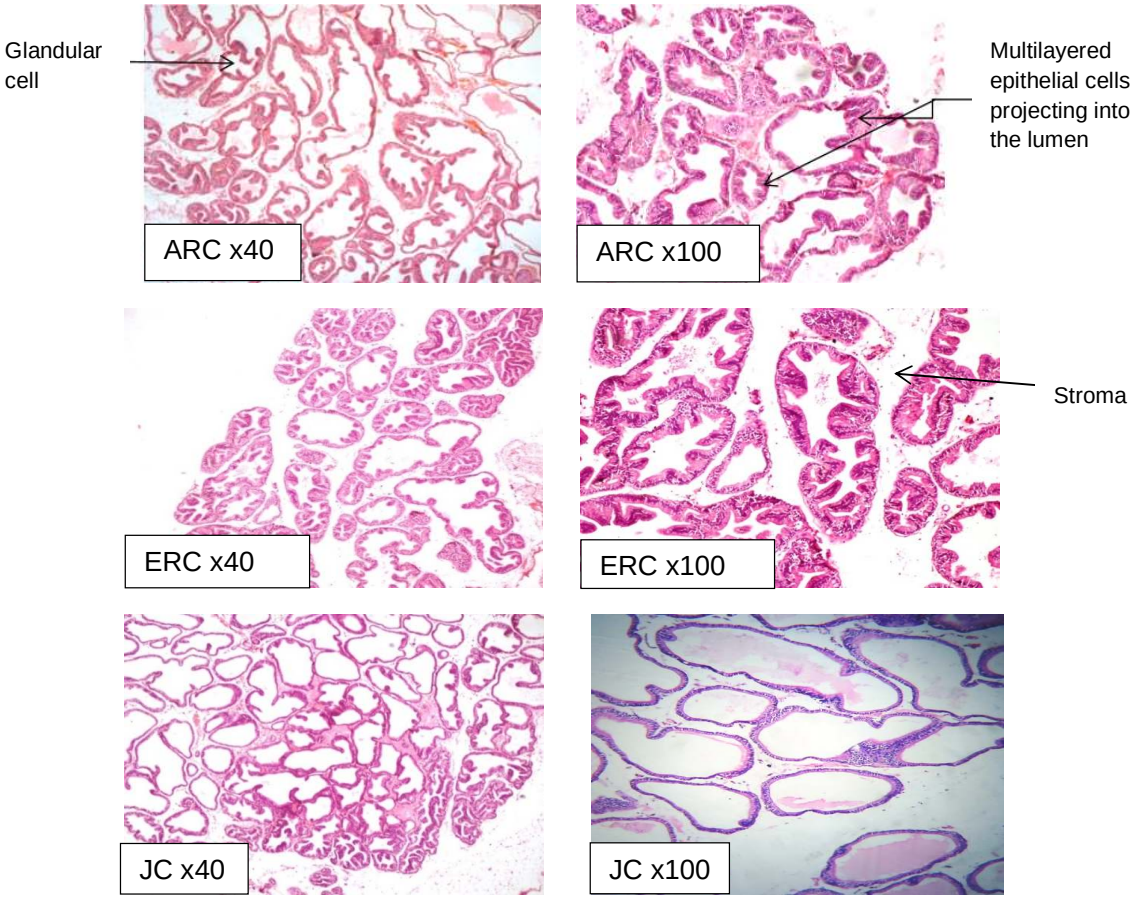

Plate 2. Sections of the prostate gland specimens from the concomitant groups (H &E)

Sections of the Aqueous Rind Concomitant (ARC) and Ethanolic Rind Concomitant (ERC) groups showed multilayered epithelium with increased stroma density; note that features of hyperplasia were of lesser magnitude in the Juice Concomitant (JC) group

due to the interplay between testosterone, oestrogen and fat deposition [26-29]. The biologically active form of testosterone that stimulates proliferation of the prostate is 5α-dihydrotestosterone (DHT) [30,31]. The prostate was stimulated in both groups; the pattern of weight change could imply that the aqueous extract of *Citrillus lanatus* probably slowed down the conversion of testosterone to DTH. Thus the exogenous testosterone might have largely been converted to estrogen which led to increased fat deposition and ultimately resulted in greater weight gain. The relevance of this inference is that incorporating *C. Lanatus* into the diet of men in the 6th decade of life which is considered as the BPH decade [1,2] may prevent the development of BPH or retard its progression. Though while the APP, whose mean weight change was significantly higher than CI, the values for the other experimental groups were higher but not statistically significant. Thus the juice or the extracts (aqueous or ethanolic) of *C. lanatus* may be capable of slowing down proliferation of the prostate gland thereby retarding the progression of BPH.

The mean prostate weights of ARP and ERP were significantly lower than that of group CI. Though that of the JC group was lower but not significant; those of ARC, ERC and JP were however higher. This finding is in keeping with results of similar studies that reported shrinkage of enlarged prostate gland following administration of pumpkin seed and oil; and *C. lanatus* [3-5,18]. In BPH, DHT is the inducer of prostatic cell. This observation could imply that the post induction administration of both extracts (aqueous and ethanolic) of the rind of *C. lanatus* was able to significantly inhibit the conversion of the exogenous testosterone to 5α-dihydrotestosterone better than concomitant administration. The symptomatology of BPH is

that of obstruction of urinary outflow and the severity of these symptoms (collectively referred to as lower urinary symptoms {LUTS}) [32] is the determinant of associated morbidity, co-morbidity and mortality. The severity of LUTS and other sequelae of BPH have a positive correlation with the size of the prostate gland [32]. The desired goal of all treatment options- drug therapy, transurethral prostatectomy (TURP) or open prostatectomy is reduction in the size of the prostate with the expectation of significant reduction in the severity of the LUTS. These treatment options have remarkable success rates with significant impact on quality of life of the patients. These therapies do not come cheap and are out of reach of majority of BPH patients from developing / undeveloped countries that constitute the continent of Africa. *Citrullus lanatus* has wider accessibility and affordability, thus the ability of its juice and its rind particularly the aqueous extract to significantly reduce the prostate weight in rats with induced BPH might make the management of BPH considerably less financially burdensome in afflicted men. Since it was the post induction groups (ARP and ERP) that had significantly shrunken enlarged prostate gland in rats, an advocacy for the inclusion of these extracts in the diet of men with clinically proven BPH may not be out of place. Vegetables rich in carotenoids have been described to have the potential of reducing the severity of BPH symptomatology [33-35]. In men with BPH, higher plasma levels of micronutrients such as lycopene, carotene, selenium vitamin E and vitamin C have been established to have a negative correlation with BPH symptomatology [36,37]. The phytoconstituents of *C. lanatus* include lycopenes, carotenoids, alkaloids, flavonoids, polyphenols, glycosides and tanins [38-40]. These phytochemicals make consumption of *C. lanatus* safe as dietary supplement, notwithstanding, those of the rind need to be determined.

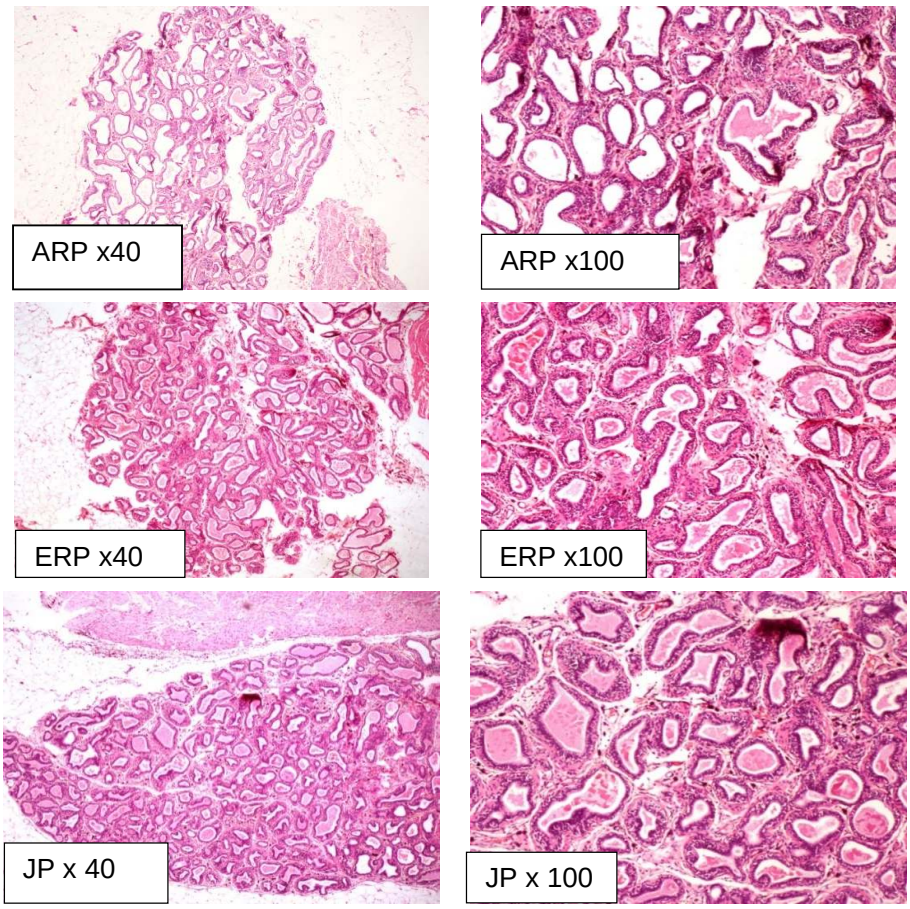

Plate 3. Prostate gland: Post-induction groups (H&E)

Sections from all the post-induction groups showed increased layering and cellularity of the epithelium. The stroma was denser with increased cellularity

Reactive oxygen species (ROS) have been implicated in the aetiology and progression of systemic diseases such as hypertension, diabetes mellitus and BPH [41]. Oxidative stress could be due to increased production of ROS or reduced depletion by antioxidants .It may even be a combination of both factors. Oxidative stress (OS) is known to induce cell proliferation and inhibit apoptosis in rat liver [42]; this may the pathway by which it contributes to prostate enlargement in BPH. Malondialdehyde (MDA) is a prooxidant. The MDA concentration of CI group was significantly higher than NC, thus the process of induction of BPH in Wistar rats was associated with increased production of prooxidant. The glutathione-S- transferases (GST) are a group of enzymes with very significant inactivation of toxic endogenous agents that are prooxidants, thus the GST are involved in cellular resistance to OS [43]. All the activities of the antioxidants (SOD, CAT & GPx) were significantly elevated in the NC group when compared with the CI. The antioxidant activities and prooxidant concentrations showed that OS is involved in induction of BPH in Wistar rats. This is in concordance with findings of related studies [41,44-46]. Groups ARC, ERP and JP had significantly lower activities of MDA than CI; thus both the juice and rind extracts of *C. lanatus* were able to ameliorate the severity of OS associated with induced BPH, with the rind having a slight edge. Most of the experimental groups had significantly higher SOD and GPx activities while only ERC and JP had significantly higher activity of CAT than CI. These results of the antioxidants demonstrate clearly the ability of *C. lanatus* to slow down the oxidative stress that has been implicated in the aetiopathogenesis of BPH [44-46]. From the results of the oxidative stress parameters, *C. lanatus* possess the property to retard oxidative stress in induced BPH in Wistar rats. Also from these results, both timing of administration (concomitant and post induction) of the interventional agents produced significant results. One of the ways aimed at early diagnosis of BPH and thus reducing its symptomatology is the screening of men aged 50 years and above. Such screening tests include digital rectal examination and prostate specific antigen assay. Though this proactive measure is commendable, not all men aged 50 years and above will develop BPH in their life time. Also when the economic status of the developing/ underdeveloped nations of Africa are factored into the discussion, then these screening procedures become of limited accessibility and affordability, hence their limitation. For any herbal medicine to be of relevance in the management of any human ailment, the timing of its administration at which it will be efficacious becomes pertinent and deserves requisite attention.

Although, the results of the oxidative stress parameters were of significance in both the concomitant and pre induction groups; those of the latter groups may be translatable into the management of BPH but those of the former groups are unlikely. This assertion is borne out of the fact that not all men aged 50 years and above will develop BPH in their life time. Herein lies the benefit of the results of the post induction groups (ARP, ERP and JP) they can thus be extrapolated to BPH management in men and incorporated into dietary schedule of BPH patients. Hence, *C. lanatus*, either its juice or the extracts of its rind (aqueous or ethanolic) have a herbal therapeutic role in the management of BPH in men.

The results discussed thus far, namely the body weights, prostate weights and oxidative stress parameters were quantitative while those of the histology of the prostate gland were qualitative assessment of the study.

Histologically, the enlarged but non-malignant prostate is characterized by proliferation of the glandular epithelium, connective tissue and smooth muscle with the latter two constituting the stroma [47,48].Sections of the prostate gland from all the experimental groups showed epithelial hyperplasia with increased stroma except for the JC group in which these features were of lesser magnitude. These histological features were similar to those observed in a study in which the extract of *C. lanatus* seed were administered to rats with induced BPH [18]. This may imply that the histological features of induced BPH in rats may require more time to revert to normal or may not revert at all. Further studies will be required to explore this postulation. The fact that the JC group showed the least epithelial and stroma proliferation could imply that the concomitant administration of the juice was the most beneficial in terms of reversing the histopathological features of induced BPH in Wistar rats.

In multi centre randomized human subject studies, the extracts of pumpkin seeds were reported to significantly reduced the prostate size, severity of urinary symptoms and improve quality of life as adjudged by increased

international prostate symptom score related quality of life [49,50].

5. CONCLUSION

Results of this study clearly showed that the rind and juice of *Citrullus lanatus* were : (1) able to reduce the enlarged prostate gland; (2) able to ameliorate the oxidative stress associated with the aetiopathogenesis of induced BPH is wistar rats and (3) able to reverse the histopathological features of the prostate in induced BPH.

On the basis of the prostate weight, the post-induction administration of the aqueous and ethanolic extracts of the rind appeared to the best in terms of efficacy. The results of the oxidative stress parameters showed all the forms of the interventional agents to be potent with no clear cut pattern.

Trial of extracts of *C. lanatus* rind and juice as herbal remedy for the management of BPH in men may give promising result like the pumpkin seed study.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The authors here declare that the study was carried out with approval of the University of Ibadan Ethical Committee on Experimental Animal. Also the “Principles of laboratory animal care” as contained in the NIH publication No. 85-23, revised 1985 were duly observed by the Authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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