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Citrus reticulata fruit peel extract ameliorates testesterone-induced benign prostatic hyperplasia-like phenotypes in rats

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ABSTRACT

Benign prostatic hyperplasia is a major pathophysiologic event that presents a high risk for prostate cancer (the second most frequently diagnosed cancer in men). The prognosis of conventional therapy for BPH remains poor due to treatment failures. Thus, natural remedies such as botanical drugs remain a promising alternative therapy to be explored for the treatment of BPH and prostate cancer. *Citrus* fruits, specifically fruit peels of *Citrus reticulata* (CRE) contain bioactive compounds that exhibit anti-inflammatory properties and have been used in crude form in traditional settings to manage benign prostatic hyperplasia and prostate cancer, however, scientific scrutiny of this ethnobotanical claim remains incomplete. This study assessed the protective effect of CRE in testosterone-induced benign prostatic hyperplasia-like phenotypes in rats. Male Wistar rats (n = 30, 150-200 g) were randomly assigned into six groups (n = 5), and treated for 28 days as follows: control group (normal saline, 5 mg/kg s.c.), model group (testosterone,5 mg/kg, i.p.), the finasteride (1 mg/kg, p.o.), and CRE (50, 100, and 200 mg/kg, p.o.) groups received testosterone (5 mg/kg, i.p.) in the morning and their respective treatments (either finasteride or CRE). All rats were given chow and water ad libitum. On the 28th day, the rats were sacrificed following deep anesthesia. Blood and the prostate gland were collected. Full blood count, serum levels of prostate-specific antigen (PSA), testosterone, C-reactive protein (CRP), and histology of the prostate gland were assessed. Compared to the model, treatment with *C. reticulata* peel extracts markedly reduced prostate weight, attenuated atresia of the prostatic glands, stromal fibrosis, and mast cell infiltration, and increased glandular secretion. Additionally, serum levels of testosterone, CRP, PSA, and white blood count were reduced in the high-dose *C. reticulata* peel extract-treated group. Fruit peels of *C. reticulata* exhibited a protective effect against BPH partly by attenuating inflammatory activity. Thus, this finding provides a rationale for further exploration of CRE for novel anti-BPH molecules that could be used to develop therapeutics against prostate cancer.

1. Introduction

Benign prostatic hyperplasia (BPH) is a major pathophysiologic event that presents a high risk for prostate cancer. Prostate cancer is the second most frequently diagnosed cancer in men and the fifth major cause of death worldwide (Rawla, 2019; Wang et al., 2022). Phenotypic hallmarks of BPH include difficulty in initiating urination, painful micturition, weak or interrupted urine flow, incomplete urinary bladder emptying, haematuria, hematospermia, and orgasmalgia (Drudge-Coates et al., 2018; Leslie et al., 2023). BPH is normally screened using a serum prostate-specific antigen (PSA) test (Armstrong et al., 2017; Tikkinen et al., 2018) and digital rectal examination (Jones et al., 2018). However, BPH is normally confirmed histologically through prostate biopsy (Streicher et al., 2019). Aside from hereditary (Ni Raghallaigh & Eeles, 2022; Vietri et al., 2021) and testosterone imbalance (Parsons et al., 2005; Xu et al., 2015), available evidence suggests that the pathogenesis of BPH involves dysregulated cell death and

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proliferation (Campbell & Leung, 2021; Kyprianou et al., 2000), inflammation (Archer et al., 2020; Shafique et al., 2012) and oxidative stress (Battisti et al., 2011; Oh et al., 2016). Thus, agents with the ability to counter the aforementioned pro-BPH defective cellular processes may hold therapeutic potential for therapy against BPH and prostate cancer. Conventionally, drugs used to manage BPH and prostate cancer in particular include anti-androgens [5-α-reductase inhibitors and α-1-adrenergic receptor antagonists] (Rashid et al., 2020; Sarkar et al., 2019; Wade et al., 2019), microtubule inhibitors [tamoxifen, vinblastine, docetaxel (Taxotere) and cabazitaxel (Jevtana)] (Clarke et al., 2019; Pienta et al., 1995; Yamamoto et al., 2023), anti-inflammatory drugs [mitoxantrone (Novantrone)] (Doat et al., 2017; Hatano et al., 2020), and DNA-modifying drugs [estramustine (Emcyt), carboplatin, oxaliplatin and cisplatin] (Corn et al., 2019; Ravery et al., 2011). Although these anti-BPH and anti-prostate cancer drugs have proven relatively effective for managing BPH and prostate cancer over the years, however, they present many setbacks. For example, these drugs do not completely cure BPH and prostate cancer. Also, these drugs have serious side effects such as reduced libido, erectile dysfunction, and nasal congestion which significantly limit their therapeutic usefulness. Similarly, the use of surgery and radiation also cause serious side effects that significantly impair the quality of life after treatment (Miernik & Gratzke, 2020). The difficulties identified with the currently available therapies for BPH and prostate cancer necessitate the need for alternative therapies preferably therapies that are not only relatively safe and organic but also easily available and cost-effective such as those derived from plants.

Plants belonging to the genus *Citrus* and family Rutaceae have several applications in ethnomedicine and the utility of various parts of these plants in ethnomedicine is gaining scientific attention lately. The genus comprises about seventeen species including *Citrus lemon* L. (lemon), *C. sinensis* L. (sweet orange), *C. reticulata* Blanco (mandarin orange, tangerine), *C. aurantium* L. (bitter orange), and *C. paradise* M. (grapefruit). Morphologically, the genus *Citrus* includes plant species (shrubs and trees) with heights spanning 3 to 15 m (Klimek-Szczykutowicz et al., 2020). The leaves are leathery and lanceolate. Depending on the species, the stems may have several branches with spines. Also, the flowers develop in leaf axils. Every flower is penta-petalous and has either white or red color. A frequently used part of *Citrus* plants is their fruits, which are hesperidium berries. *Citrus* fruits have diverse applications due to their nutritional and extra-nutritional (cosmetic and pharmaceutical) qualities. Geographically, *Citrus* sp. are distributed naturally in warm and tropical ecological regions, including Africa and the Mediterranean (Klimek-Szczykutowicz et al., 2020).

Different parts of *Citrus* plants, such as fruits, fruit peels, leaves, and seeds, are used traditionally to treat various forms of diseases. The fruit peels of *C. reticulata* are traditionally used as tonic, stomachic, astringent, carminative, and skin care. Also, the dried fruit peels of *C. reticulata* are used to improve digestion and reduce phlegm (Lv et al., 2015). The medicinal uses of *C. reticulata* are attributed to its rich phytochemicals which have diverse bioactivities including anti-fungal, anti-bacterial, anti-hyperalgesia, anti-oxidant, and anti-inflammatory properties (Klimek-Szczykutowicz et al., 2020). Extracts from *C. reticulata* fruit peels were shown to antagonize lipopolysaccharide (LPS)-induced production of nitric oxide in macrophages (Zhang et al., 2022). This observation is indicative of the potential anti-inflammatory properties of *C. reticulata* fruit peels. Additionally, a polymethoxylated flavone, nobiletin, derived from the fruit peels of *C. reticulata* exhibited neuroprotection in a rat model of Parkinsonism (Jeong et al., 2015) and ameliorated memory impairment in a rat model of Alzheimer's disease (Kimura et al., 2018), highlighting the potential of mitigating age-related disorders. Also, two flavonoids, tangeretin, and nobiletin, that are derived from the fruit peels of *C. reticulata*, inhibited cancer growth in vivo, and also effectively inhibited the proliferation and blocked cell cycle progression at the G1 phase in colon and breast cancer cell lines (Morley et al., 2007). Furthermore, tangeritin caused apoptosis in HL-60 cells (human promyelocytic leukemia cells) but not in human peripheral mononuclear cells (Hirano et al., 1995), highlighting selective toxicity of the flavonoid against cancerous cells. This observation suggests that the fruit peels of *C. reticulata* could prevent prostate cancer initiation. Therefore, this study investigated the effect of *C. reticulata* fruit peel extract (CRE) against testosterone-induced BPH-like phenotypes in rats as well as the possible phytochemical composition of CRE.

2. Materials and methods

2.1. Drugs and chemicals

Testosterone propionate, finasteride, and ethanol were obtained from the Center for Plant Medicine Research (CPMR), Akuapem-Mampong, Eastern Region, Ghana. The animal experimentation and extraction were carried out at the laboratories of the CPMR. Biochemical assays and hematological analyses were performed at the laboratories of the University of Ghana Medical Center, Accra, Ghana.

2.2. Collection and identification of plant material

Fruits of *C. reticulata* were obtained from local farmers in Mankesim village, Central Region, in January 2022. The sample was identified, confirmed, and authenticated by Mr. Francis Otoo, a botanist at the Herbarium of the School of Biological Science, University of Cape Coast where a voucher specimen was deposited (https://ir.ucc.edu.gh/xmlui/handle/123456789/8598).

2.3. Preparation of C. reticulata fruit peel extract

The *C. reticulata* fruit peel extract was prepared as described previously (Boye et al., 2024) with slight modifications. Briefly, the peels of the *Citrus* fruits were removed and dried at room temperature after washing the fruits under tap water. A known mass of the dried peels was grounded using an electrical blender (Philips HL7777-00) after which soxhlet extraction was performed on the resultant powder. The powder was placed in the thimble, which was then placed in a distillation flask containing ethanol (200 ml). The ethanol was heat-refluxed for 12 h during which the vapor extracted solutes from the powder into the bulk ethanol in the distillation flask. The ethanol-turned extract was placed in a desiccator. After complete drying, the final crude ethanol extract of *C. reticulata* fruit peel was code-named CRE. The extraction process was repeated several times to obtain more CRE. CRE was stored in a refrigerator at –20 °C until use.

2.4. Animal acquisition and husbandry

Thirty (30) male Wister albino rats aged 10-15 weeks and weighing 150-200 g were purchased and housed in cages at the Animal Holding Facility of CPMR. The rats were kept in well-ventilated cages at normal room temperature (35-37 °C) and humidity and fed with regular laboratory chow (Grower mash, Sankofa) in a sipper bottle/spill-proof bowl. Animal experiments, procedures, and techniques were done according to institutional, national, and

international guidelines concerning the use of animals in scientific experimentation.

2.5. Establishment of testosterone-induced prostatic hyperplasia in rats

Benign prostatic hyperplasia was induced in rats as previously described by Cai et al. (2018) with slight modifications. The rats were randomly assigned into six groups. Except for the control rat group, the five rat groups were anesthetized with phenobarbital injection (50 mg/kg, i.p.), right and left testicles were removed aseptically. The rats were then intraperitoneally injected with 5 mg/kg testosterone propionate for 28 days and concurrently treated with either CRE or standard drug (Finasteride, 1 mg/kg, p.o.). Additionally, rats that did not receive testosterone injection served as controls. The experimental groups were:

- Control group: Rats in the control group received normal saline (5 mg/kg, i.p.) daily in the morning for 28 days.
- Model group: Rats in this group were intraperitoneally injected with testosterone propionate (5 mg/kg, i.p.) in the morning for 28 days without any other treatment.
- Finasteride (1mg/kg, p.o.) group: Rats in this group received intraperitoneal testosterone propionate (5 mg/kg, i.p.) injection in the morning and finasteride (1mg/kg, p.o.) in the afternoon for 28 days.
- CRE (50 mg/kg, p.o.) group: Rats received testosterone propionate injection (5 mg/kg, i.p.) in the morning and CRE (50 mg/kg, p.o.) in the afternoon for 28 days.
- CRE (100 mg/kg, po) group: Rats received testosterone propionate injection(5 mg/kg, i.p.) in the morning and CRE (100 mg/kg, p.o.) in the afternoon for 28 days.
- CRE (200 mg/kg, po) group: Rats received testosterone propionate injection(5 mg/kg, i.p.) in the morning and CRE (200 mg/kg, p.o.) in the afternoon for 28 days.

2.6. Body weight measurement

The body weight of rats was determined weekly throughout the study. On the last day, following overnight fasting and testosterone propionate injection, the rats were anesthetized before sacrifice.

2.7. Biochemical analysis of blood

Blood was collected into labeled EDTA anti-coagulant tubes for full blood count using (Mindray BS200) and labeled Gel tubes for biochemical analysis namely testosterone, C-reactive protein, and prostate-specific antigen (PSA).

2.8. Serum PSA measurements

Serum PSA was determined using the Enzyme-Linked Immunosorbent Assay (ELISA) kit as described previously (Dalal et al., 2022). Serum samples or standards (0, 2.5, 5.0, 10, 25, and 50 ng/ml of PSA) (v = 25 µl) were placed in wells of 96-well plate pre-coated with HRP-labeled anti-mouse PSA (v = 100 µl) after which the plate was incubated at 20-25 °C for 30 min. The wells were washed thrice with 300 µl of a reconstituted washing buffer. A 100 µl substrate-reagent mixture consisting of TMB (3,3′, 5,5′-tetramethylbenzidine) (1.2 mM) and hydrogen peroxide (≤ 6.0 mM) was then added to each well and the total mixture was thereafter incubated for 15 min at 20-25 °C. The reaction was halted using 100 µl of a stop solution (0.5 M sulphuric acid) and the absorbance of the reaction mixture was measured subsequently at a wavelength of 450 nm using a Urit 680 microplate analyzer. The straight-line graph was plotted using the various standard concentrations (as abscissa) and their respective absorbance (as ordinate). The serum PSA concentration was subsequently determined using an equation of the linear graph.

2.9. Serum testosterone level

Serum testosterone level was determined using enzyme immunoassay as described previously (Njoroge et al., 2015). Goat anti-rabbit IgG-coated wells of a 96-well plate were filled with 150 µl of a reaction mixture, consisting of rabbit anti-testosterone reagent and testosterone-HRP conjugate (1:2). A 100 µl of either testosterone standards or serum was added to the wells after which the plate was incubated for 90 min at 37 °C. The wells were rinsed thrice with washing buffer (1x). TMB substrate(100 µl) was added to the reaction mixture and after 10 seconds, the plate was incubated for 20 min at room temperature (18-22 °C). A 100 µl stop solution was added to the wells and the absorbance of the reaction mixture was read within 15 min at 450 nm using a microfilter well reader.

2.10. Histological assessment of prostate tissues using Gleason score

Prostate glands were dissected out, weighed, and preserved in 10% formalin solution. The fixed prostate gland was sliced and the slices were dehydrated in increasing gradient concentrations of ethanol, cleared with xylene, and embedded in paraffin wax. Thin tissue sections (4-5 µm) were cut from the paraffin-embedded tissue blocks using a microtome (Leica Histocare Autocut), treated with hematoxylin and eosin stains and mounted on the slide using DPX. Images of the five fields of the dorsal lobes of the mice's prostate glands were captured using a bright field binocular microscope connected to a high-resolution camera. After the histological assessment, the micrographs were graded by a pathologist who did not know the different treatment groups. The International Society of Urological Pathology (ISUP)-modified Gleason grading (Epstein et al., 2016) was used to grade the histology of the prostate gland according to the criteria described in Table 1.

Table 1. The International Society of Urological Pathology (ISUP)-modified Gleason grading

Characteristics	Score
Small invariable glands	1
More interglandular stroma	2
Distinctively invasive margins	3
Asymmetrical masses of neoplastic glands	4
Only seldom gland formation	5

Briefly, the most common pattern (primary or dominant) was graded after which the next common pattern (secondary or subdominant) was graded. The grades for the two patterns were summed to get the Gleason score for the prostate gland.

2.11. Statistical analysis

Graph Pad Prism 8.0 (GraphPad Software, Inc., La Jolla, CA, USA) was used for statistical analyses. Except for the data on the Gleason scores which were reported as medians, all other data were expressed as mean ± standard deviation. Comparisons of group data were done using one-way ANOVA followed by a post hoc test (Dunnett's test). The Kruskal-Wallis test was used to assess the differences among the median scores. *p*-value less than 0.05 was considered statistically significant.

3. Results and discussion

C. reticulata fruit peel extract demonstrated prophylactic potential against experimentally-induced androgen-dependent prostate cancer, which is one of the most frequent malignancies in older men. Testosterone propionate was used to induce prostatic hyperplasia phenotype in Wistar rats. Testosterone binds and activates the androgen receptor (AR) in the prostate gland. A testosterone-androgen receptor complex forms which is then translocated to the nucleus to activate genes that promote the survival and proliferation of prostatic cells (Gerald & Raj, 2022). Additionally, prostate gland pathophysiology involves inflammation, which is inducible by hypertestosteronemia. In this study, the anti-BPH effect of CRE was assessed by measuring serum levels of testosterone, PSA, and C-reactive protein (CRP), determining full blood count (FBC), and also assessing the histological architecture of the prostate gland. The findings from this study suggest that *C. reticulata* fruit peel extract could delay the progression of prostate cancer.

3.1. Phytochemical composition of CRE

The bioactivity of plant extracts is attributable to myriads of secondary metabolites that are present. Phytochemical screening of CRE showed the presence of secondary metabolites, namely flavonoids, tannins, alkaloids, terpenoids, and saponins. The anti-inflammatory, antioxidant, and anti-tumor properties of all the identified secondary plant metabolites in CRE (Table 2) have been demonstrated, but in other *Citrus* plants. These suggest that the observed phytochemical signature may be a shared characteristic of all the plant species in the genus *Citrus*. More so, prostate cancer pathophysiology involves oxidative stress, inflammation, and proliferation (Archer et al., 2020; Battisti et al., 2011; Campbell & Leung, 2021; Kyprianou et al., 2000; Oh et al., 2016; Shafique et al., 2012), and thus CRE have the potential to mitigate prostate cancer progression. The prophylactic prostate-protective effects of CRE were expected given its phytochemical signature.

Table 2. Phytochemical composition of CRE

Secondary plant metabolites	Phytochemical test	Reference	Results
Alkaloids	Dragendorff's test	Tanzey et al. (2020)	+
Tannins	$FeCl_3$	Kuntal et al. (2018)	+
Flavonoids	Sodium hydroxide test	Barupal et al. (2019)	+
Terpenoids	Salkowski test	Abdel-Rahman et al. (2019)	+
Saponins	Foam test	El Hazzam et al. (2020)	+

+ = qualitatively detected, CRE = *C. reticulata* fruit peel extract

3.2. Effect of CRE treatment on changes in body and prostate gland weights

Benign prostatic hyperplasia is characterized by an increase in prostate weight, which could be detected in a digital rectal examination during the screening process. An increase in prostatic weight is a crucial indicator of the start of benign prostatic hyperplasia (Akanni et al., 2020). Rats in the model group significantly recorded a higher percentage loss in body weight relative to the rats in the control group. However, relative to the model group, the finasteride-treated and CRE-treated testosterone-injected rats gained weight. The mean weight of the prostate gland was increased in the model group relative to the control group. Relative to the model group, treatment with finasteride and CRE decreased the weight of the prostate gland (Figure 1). Prostate weight and size increases are a direct result of testosterone's crucial role in the development of the prostate gland (Li et al., 2018). In this study, the model group exhibited an increase in prostate weight, which was attenuated after treatment with CRE, highlighting the anti-prostate cancer potential of *C. reticulata* fruit peel extract.

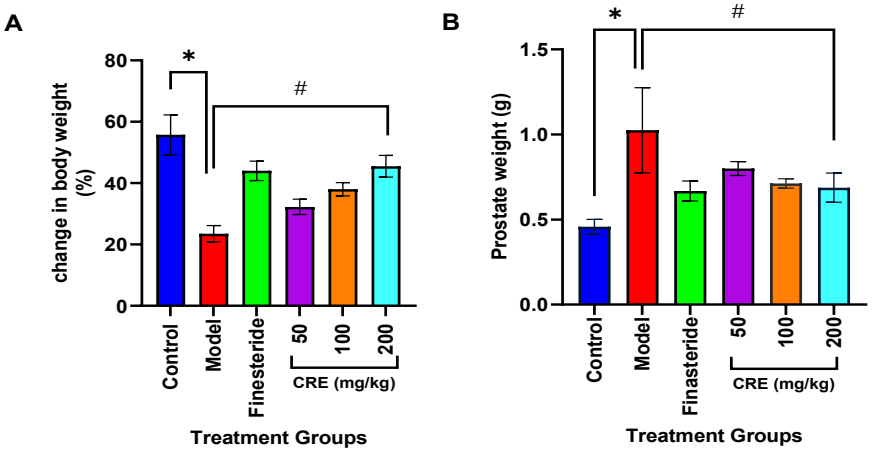

Figure 1. Effect of CRE treatment on body weight and prostate weight

3.3. Effect of CRE on the histology of testosterone-induced BPH

Benign prostatic hyperplasia is confirmed via histological assessment of a prostate biopsy. In this study, there were marked changes in the histological architecture of the prostate gland in the model group relative to the control. Relative to the control group, the model showed shrunken prostate glands with scanty secretions, increased interstitial fibrosis, and mast cell infiltration, indicative of inflammatory processes in the model group (Figure 2). Additionally, the epithelia of the prostate glands were markedly different from

that of the normal rats, indicative of poorly differentiated prostate glands. CRE dose-dependently preserved the prostate gland histology. In the peel extract-treated group, the prostate gland exhibited increased prostatic secretion and reduced stromal fibrosis, indicative of the therapeutic potential of CRE. Additionally, the columnar cells lining the prostate gland appeared closer to the control relative to the model, indicative of at least a moderately differentiated prostate gland (Figure 2). These observations suggest a histoprotective potential of the peel extract in prostate cancer.

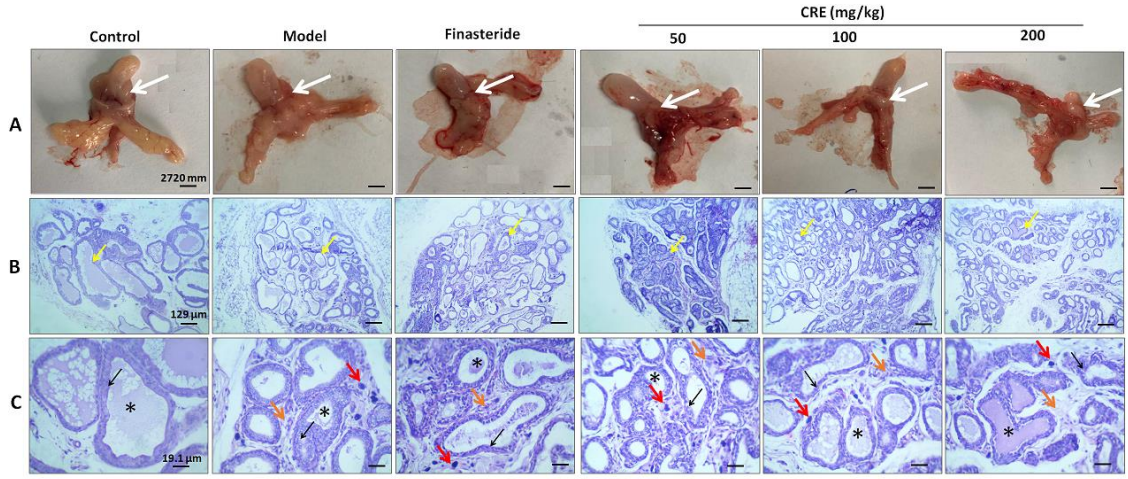

Figure 2. Effect of treatments on gross (A) and histopathological appearance (B&C) of the prostate

Treatment groups: Control group, model group, finasteride group, CRE group (50 mg/kg), CRE group (100 mg/kg), CRE group (200 mg/kg). The yellow arrow represents prostatic glands, The black asterisk (*) represents prostatic secretion, the black arrow represents epithelial cells of the gland, the red arrow represents mast cells, and the brown arrow represents lymphocytic infiltration. CRE: *C. reticulata* fruit peel extract.

Also, histological grading of prostate cancer is a powerful prognostic indicator for clinically localized prostate cancer and is one of the most vital factors in determining the course of patient management. In this study, the 2014 ISUP-modified Gleason grading system was used to assess the histology of the prostate glands (Epstein et al., 2016; Humphrey, 2017). The grading system reports the sum of the scores for the dominant gland pathology and the subdominant gland pathology (Delahunt et al., 2012; Humphrey, 2017), highlighting the usefulness in tracking the progress of the disease. The model group had a Gleason score of 10, with scores of 5 and 5 for dominant and subdominant pathologies, respectively. The finasteride-treated group had a Gleason score of 6, with scores of 3 and 3 for dominant and subdominant pathologies, respectively. The low-dose, middle-dose, and high-dose CRE-treated groups had Gleason scores of 9, 7 and 7, respectively. The dominant and subdominant pathologies of CRE-treated groups were 5 and 4 for low dose, 4 and 3 for middle dose, and 3 and 4 for high dose (Figure 3).

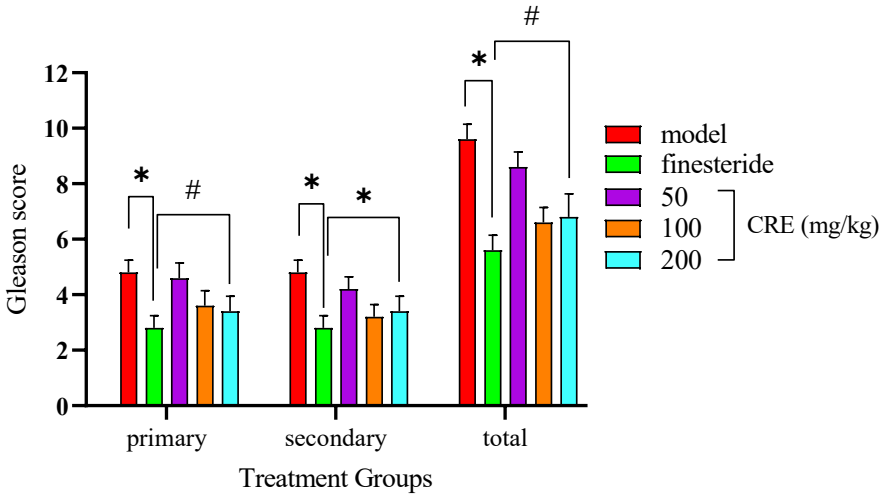

Figure 3. Assessment of the effect of CRE on prostate histology using Gleason score

In this study, the model group recorded median scores of 5 for both dominant and sub-dominant pathologies. The median scores for dominant and subdominant pathologies of CRE-treated groups were 5 and 4 for low dose, 4 and 3 for middle dose, and 3 and 4 for high dose, indicating the histoprotective potential of CRE (Figure 3).

3.4. Effect of CRE on full blood count

Clinicians monitor prostate cancer using a plethora of serum markers including testosterone and prostate-specific antigen (PSA). Testosterone is the predominant male androgen and high serum levels of testosterone increase the risk of developing prostate

cancer; hypertestosteronemia promotes the proliferation of the prostate gland. Additionally, extraprostatic organ damages, involving the kidney and liver, occur in hypertestosteronemia.

PSA is a glycoprotein enzyme secreted by the epithelial cells of the prostate gland (Duskova & Vesely, 2015). Assaying serum levels of PSA is useful in prostate cancer detection and patient treatment and monitoring. The serum PSA levels of men with healthy prostates are minute, but is often elevated in prostate cancer or other prostate disorders (Mazzucchelli et al., 2000). In this study, the model groups recorded high levels of serum testosterone and prostate-specific antigen (PSA) (Figure 4), highlighting the increased risk of the model group to developing prostate cancer and hyper testosterone-associated extra-prostatic damage. Treatment of the model rats with CRE decreased the serum levels of testosterone and PSA, indicative of the protective effect of CRE.

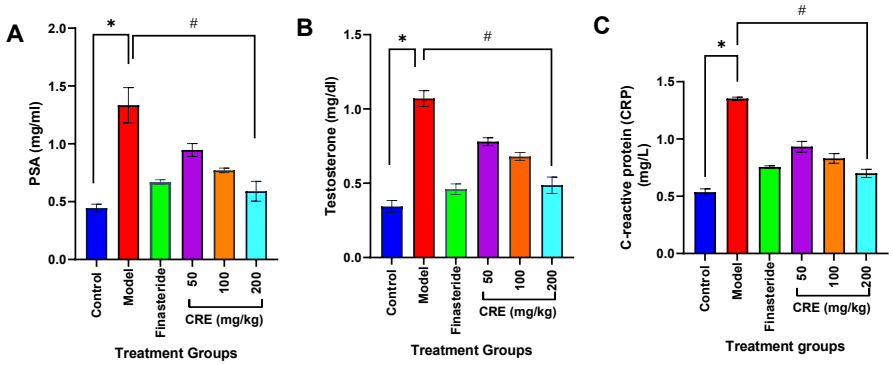

Figure 4. Effect of CRE on PSA, testosterone, and C-reactive protein levels
Each value is the mean ± SD, $n = 3$. # $p < 0.05$ (treatment versus model groups); * $p < 0.05$ (control versus model groups)

Inflammation is one of the mechanisms that underlie the pathophysiology and progression of prostate cancer and other cancers (Libby, 2007). Several indicators, including C-reactive protein (CRP), a ring-shaped pentameric protein, and white blood cell count are used in the clinical setting to assess the inflammation status of cancer patients. Serum CRP levels rise in response to inflammation, which is associated with an increased risk of developing BPH (O'Brian et al., 2021). In this study, serum CRP level was increased in the model group after testosterone induction. Additionally, the stroma of the prostate gland from the model group exhibited massive infiltration of mast cells (Figure 2) and higher counts of WBC (Figure 5), which were attributable to elevated counts of lymphocytes, monocytes, and neutrophils (Figure 5). The changes in the aforementioned variables underscore the involvement of inflammation in prostate cancer pathophysiology, thus reduction in inflammation could delay cancer progression. CRE decreased mast cell infiltration of the prostate gland stroma, and reduced blood counts of leukocytes, neutrophils, lymphocytes, and monocytes as compared to the model group, highlighting the anti-inflammatory potential of CRE in mitigating BPH.

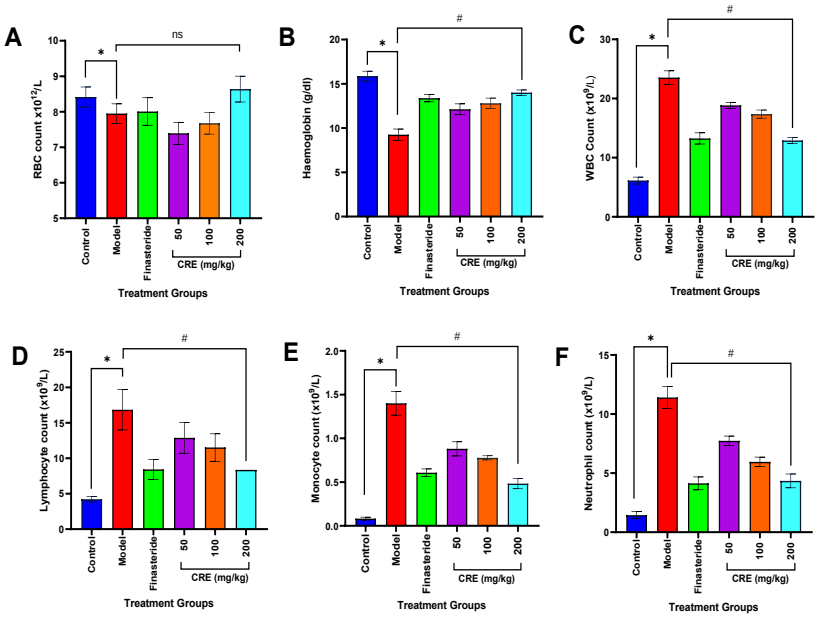

Figure 5. Effect of CRE on full blood count (FBC)
Hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, lymphocyte count, monocyte count, neutrophil count. Each value is the mean ± SD, $n = 4$. # $p < 0.05$ (control versus model groups); * $p < 0.05$ (treatments versus model groups). CRE: *C. reticulata* fruit peel extract

The findings of this study provide a scientific context and rationale for further incremental studies on CRE concerning BPH and prostate cancer even though the study could not benefit from additional assessments such as immunohistochemistry of the prostate gland, use of flow cytometry to monitor cell proliferation, and cell cycle arrest status. Notwistandingly, the present finding provides the basis for additional future studies as well as the generation of new scientific questions to drive the direction of future studies.

4. Conclusions

C. reticulata fruit peel extract prevented the exercabation of testosterone-induced BPH-like phenotypes in rats. The anti-BPH activity of CRE could be attributed partly to its anti-inflammatory phytochemical components. Thus, this finding provides a rationale for further exploration of CRE for novel anti-BPH molecules that could be used to develop therapeutics against prostate cancer.

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Conflict of interest

The authors declare that they have no known competing financial interest or personal relationships that could have appeared to influence the work reported in this paper.

Statement of ethics

All animal experiments and procedures used in this study were in full compliance with standard institutional (UCCIRB/CHAS/2022/90), national, and international guidelines (Guide for the Care and Use of Lab Animals, NIH publication No. 85-23) regarding the use of animals in scientific experimentation.

Availability of data and materials

All data generated or analyzed during this study are included in this published article. On request, the associated author can provide more information.

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CRediT authorship contribution statement

Alex Boye: Conceptualization, Investigation, Data curation, Writing - original draft, Supervision
Samuel Essien-Baidoo: Resources, Conceptualization, Visualization, Formal analysis, Investigation, Methodology
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Supplementary File

None.

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