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Research Article

Preventive effect of Dinoprostone (Prostaglandin E2) on testosterone-induced prostatic hyperplasia in a rat model

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Abstract

Background: Benign prostatic hyperplasia (BPH) is a popular age-linked ailment featured by prostatic enlargement and urinary obstruction. Dinoprostone (DINO) is prostaglandin E_2 having anti-proliferative and anti-inflammatory actions.

Objective: This research attempted to assess the effect of DINO vs. finasteride (FINA) on testosterone (TEST)-induced BPH in rats.

Methods: 40 adult male rats were haphazardly separated into 4 groups (n = 10); namely control, TEST, TEST + FINA, and TEST + DINO. BPH was induced with subcutaneous TEST (3 mg per kg per day) for 4 weeks. FINA (5 mg per kg) and DINO (7 mg per kg) were delivered orally.

Results: TEST administration led to marked prostatic enlargement and hyperplasia, paralleled by remarkable elevations in PCNA, DHT, 5α-reductase, β-catenin, ERβ, pro-inflammatory IL-6, and pro-fibrotic TGF-β and VEGF mediators. FINA and DINO effectively attenuated these alterations, restoring prostate weight and histoarchitecture, downregulating β-catenin and ERβ, ameliorating PCNA expression, and suppressing DHT and 5α-reductase activity. Both drugs modified inflammatory and angiogenic mechanisms and corrected PPAR-γ expression and regulated BCL-2 levels, indicating diminished apoptosis. While FINA surpassed DINO in inhibiting DHT, IL-6, and β-catenin expression, both treatments were equally effective in terms of anti-hypertrophic, anti-inflammatory, and anti-angiogenic actions.

Conclusions: DINO demonstrated promising anti-BPH effects comparable to FINA, acting via EP receptor-mediated modulation of prostatic growth and inflammation. These findings are viewed as preliminary and warrant further investigations of DINO for BPH treatment.

Keywords

Dinoprostone, Prostaglandin E2, Benign prostatic hyperplasia, Finasteride, Dihydrotestosterone, inflammation

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PENSOFT

Introduction

Benign Prostatic Hyperplasia (BPH) is a disorder phenomenon bedeviling public health throughout the world and is often defined essentially as a true hyperplastic process with glandular-epithelial and stromal/muscle tissue non-malignantly growing within the prostatic transition and periurethral zones (Ng et al. 2025). BPH represents a histogenically genuine prostatic enlargement, distinct from benign prostatic enlargement (BPE), yet it can ultimately lead to bladder outlet obstruction (BOO), thus leading to the cluster of problems characteristic of Lower Urinary Tract Symptoms (LUTS) (Patel and Parsons 2014). Degree of interdependence exists between histological manifestations and clinical presentation of BPH; they are nonetheless not identical. This means that the presence of one manifestation does not necessarily imply the existence of the other. The condition has very unclear causes, although chronic localized inflammation is commonly seen histologically, which may be the result of low-grade prostatitis or autoimmune disorders and contributes significantly to the overall pathology (Oseni et al. 2023; Kaltsas et al. 2025; Ng et al. 2025). The vast and continuously increasing patient pool demands therapeutic strategies that prioritize long-term safety and tolerability under optimal patient compliance.

Standard pharmacological treatment for BPH and associated LUTS mainly uses two major classes of drugs targeting the two distinct physical components of obstruction. α1-adrenolytics (alpha-blockers) act by relaxing adrenergic receptor-mediated prostatic vascular contractility, the dynamic component of obstruction, facilitated by augmented α-adrenoceptor signaling (Schwinn and Roehrborn 2008). On other hand, 5-alpha reductase inhibitors (5-ARIs) address the static component by decreasing prostate hyperplasia through blockade of the transition of testosterone into dihydrotestosterone (DHT) (Chislett et al. 2023). Even though these therapies are often used in combination to enhance clinical efficacy, their long term success is severely impeded by their side effect profiles, which are often intolerable and debilitating (McVary 2007; Naji et al. 2022). However, existing therapeutic strategies seriously compromise the quality of life. 5-ARIs commonly cause alterations in sexual function, which might include diminished sexual drive, erection problems, reduced ejaculate volume, and gynecomastic complications linked to reduced DHT levels and subsequent estrogen shunting because they interfere with endocrine function (Gur et al. 2013). The increased clinical concern holds over adverse neurocognitive and psychiatric effects related to chronic exposure to both α-blockers and 5-ARIs, for which survey and self-report instruments typically identify memory loss, general confusion, depression, and anxiety (Trost et al. 2013; Ali et al. 2025). Such serious drug-related problems (DRPs) directly correlate with an unacceptable failure in therapeutic adherence (Cindolo et al. 2015). Low adherence, systemic side effects of targeting both the adrenergic and androgenic axes, and this certainly provides us an essential research question on unmet medical needs in BPH that need urgent explorative ventures into alternative and perhaps nonhomeostatic signaling pathways for developing further therapeutics.

Pathway manipulation of prostaglandin signaling is a highly dynamic means to modulate the underlying pathophysiology of BPH. Dinoprostone is one of the naturally occurring prostaglandins E2 (PGE2), an eicosanoid that can potentially invoke nearly all necessary functions, from inflammation to smooth muscle tone, through mediation of at least four GPCR subtypes EP1, EP2, EP3, and EP4 (Fujino et al. 2003; Sugimoto and Narumiya 2007; Kawahara et al. 2015). That makes this target highly relevant for the treatment of BPH in that it has been long recognized as controlling smooth muscle tone in many organ systems, The vascular and reproductive tracts included (Martinez-Cutillas et al. 2014).

PGE2 is found to mediate concentration-dependent inhibition of nerve-mediated contractile responses in vitro in isolated rat prostate tissues: indicative of prostatic smooth muscle relaxation (Zhao et al. 2021). The pharmacological characterization therefore would pinpoint smooth muscle inhibition towards mediating through the EP2 subtype receptor. This receptor-mediated signaling pathway specifically showed this relaxation action, as opposed to those prostanoids and other EP receptor types as well (Martinez-Cutillas et al. 2014). Hence, it establishes a new non-adrenergic mechanistic ground for examining the potentialities of using dinoprostone and selective EP2 agonists in alleviating the obstruction caused by BPH dynamic. The exceedingly specific nature of this inhibitory effect implies a possible translational strategy in targeted pharmacologic modulation of EP2 signaling to counter the debilitating side effects that arise from systemic adrenergic interferences inherent to α-blockers.

While the relaxation of prostatic smooth muscle mediated by the EP2 receptor is therapeutically attractive, any study on dinoprostone must seriously consider its widely acclaimed and well-documented roles in cell proliferation, cell survival, and tumorigenesis in an extensive array of tissues (Wang et al. 2015; Karpisheh et al. 2019; Sohrab et al. 2023). The majority of PGE2 transmission is executed via EP2 and EP4 receptors, whose activation is connected with the Gs protein, which in turn augments the intracellular level of cyclic adenosine monophosphate (cAMP) and necessitates a corresponding stimulation of the protein kinase A (PKA) pathway (Quan et al. 2013). This inherently is a pro-survival pathway, against apoptosis, as demonstrated in models such as gastric mucosal cells.

This new therapeutic use of the EP2 signaling, however, faces a fundamental challenge from the now accepted view of the PGE2-EP2/4 axis in inducing proliferation and hyperplasia in the prostate gland (De Paz Linares et al. 2021). Based on this principle, we hypothesize that dinoprostone, through EP2-selective modulation, may exert therapeutic potential in the management of BPH.

Materials and methods

Experimental rats

Forty adult male Sprague-Dawley rats (2.5–3 months of age at a starting weight of 210–250 g) were purchased from the Animal Facility, College of Veterinary Medicine. The animals were kept under standardized laboratory conditions in polypropylene cages containing five rats each. Maintaining ideal environmental parameters, a thermal spectrum of 22–26 °C, ambient humidity under controlled levels, and a 12 h light/12 h dark schedule. Ventilation was provided through a negative-pressure air exchange system. Standard laboratory chow and fresh tap water were made freely available. Before commencing the experimental procedures, all subjects were allowed to acclimatize for a period of one week. The research proposal has been evaluated and authorized by the Institutional Animal Care and Use Committee.

Experiment design

The present pharmacological agents include testosterone (Cat. No. 86500), finasteride (Cat. No. F1293), and dinoprostone (Cat. No. D2250000). All the above were sourced from Merck, Darmstadt, Germany. This study was designed to show whether finasteride and dinoprostone have modulatory effects on testosterone induced BPH in the male rat. The experimental design involved a total of 40 animals arbitrary allocated into 4 groups, with 10 subjects in each group. BPH was evoked via the subcutaneous administration of testosterone at a dosage of 3 mg per kg per day for 4 consecutive weeks (Li et al. 2018; Ali et al. 2026a). The corresponding test compounds are administered once daily orally, given one hour before testosterone injection to ensure appropriate pharmacological interaction. Phosphate-buffered saline (PBS, 1 mL/kg/day) was given to the Normal control (N) group, which served as a baseline reference. The Positive Control (TEST) group submitted to induction of BPH by means of subcutaneous injection of the testosterone (3 mg/kg/day) plus intraperitoneal phosphate-buffered saline (PBS, 1 mLper kg per day) as vehicle. The TEST+-FINA (Standard) group, after receiving testosterone, was given finasteride by mouth at the dose of 5 mg/kg/day dispersed in 2.5% ethanolic solution. The TEST+DINO group received oral dinoprostone at the dose of 7 mg per kg per day, prepared in a solvent mixture of ethanol and dimethyl sulfoxide (DMSO), along with testosterone.

Dinoprostone was initially dissolved in small amounts of ethanol and DMSO before being diluted with PBS to the appropriate working concentration. The final solvent concentrations were kept to a minimum to minimize any possible biological effects, in line with widely used vehicle systems in rodent pharmacological studies.

We investigated the effects of four weeks, as the duration of treatment was based on an established experimental timeframe for testosterone-driven BPH development in rat models (Jasim et al. 2025; Ali et al. 2026b). Dinoprostone dosage (7 mg/kg/day) was chosen thanks to past pharmacological studies examining prostaglandin-mediated signaling in rodent systems, which generated measurable biological activity without any serious drug-related toxicity (Guzman et al. 2025). Preliminary pilot observations before the current trials also aided in establishing these dosages in prostatic tissues with no deleterious effects on treated animals.

The group distribution are detailed in Table 1.

Table 1. Experimental groups.

Group	Treatment description	Treatment details
Normal Controls (N)	Negative control	No treatment administered
Model/ induction Controls (T)	Testosterone-induced BPH + vehicle	S.C. testosterone (3 mg per kg per day) + i.p. PBS (1 mL per kg per day)
T+FIN (Standard)	Testosterone + Finasteride	Oral finasteride (5 mg/kg/ day) disintegrated in 2.5% ethanol, utilized with testosterone
T+DP	Testosterone + Dinoprostone	Oral dinoprostone (7 mg per kg per day) dissolved in ethanol, DMSO, and dimethylformamide, applied with testosterone

Sample and tissue collection

The animals were sacrificed with ether; blood samples were gathered through cardiac puncture for serum analysis seventy-two hours after last testosterone injection. Immediately after dissection, the prostatic tissues were excised and carefully cleared of adhering fat and connective tissue. Tissues were gently blotted dry with sterile filter paper to eliminate excess fluid before processing. Each specimen systematically was divided into defined portions given for biochemical, molecular, and histological evaluations. Snap freezing in liquid nitrogen, halting all enzymatic activity, was done for those stored at –80 °C until analysis for biochemical and molecular assays (Alzubaidy et al. 2020; Idan et al. 2024; Farooq Ali et al. 2025).

Prior to use, tissues were homogenized mechanically on ice in a pre-chilled homogenization buffer with protease and RNase inhibitors protecting the integrity of both protein and nucleic acid material. The homogenates were then spun at 10,000 × g for 15 min at 4 °C to discard insoluble materials. The resulting supernatants are very rich in soluble cytosolic particles that will be employed directly for ELISA and techniques for nucleic acid isolation procedures (Luty et al. 2025b; Motib et al. 2025).

Fixation of the tissue was done in 10% freshly prepared neutral-buffered formalin for 24 hours, in parts for histopathological and immunohistochemical analysis, to prevent loss of structure and antigen. Following fixing, prostatic tissues were dried using different grades of ethanol, cleaned with xylene, and coated with paraffin (Mohammed et al. 2022; Attarbashee et al. 2025a). A rotating handheld microtome was set up to obtain sequential seg-

ments with a 4–5 μm thickness, which were then placed on transparent slides covered with poly-L-lysine for improved stickiness. These were further subjected to histological staining and immunohistochemical analysis.

Prostate weight determination and prostatic index measurement

Body weights were recorded at the beginning and the end of the experiment to monitor weight changes related to treatment. The prostatic index (PI), computed as the prostatic weight relative to body weight (mg/g), was used to quantify enlargement of the prostate.

Histopathology investigations of prostatic tissues

Using light microscopy at 400× magnifications, microscopic changes to glandular and stromal architecture were observed on stained sections. Specific histopathological attributes of BPH were assessed: epithelial hyperplasia with excessive layering of epithelial cells with papillary infoldings into the gland lumina; stromal proliferation with fibromuscular thickening; and infiltration of interstitial tissue with inflammatory cells. The severity of hyperplastic changes was also qualitatively examined based on the degree of epithelial thickening, luminal dilation, and glandular crowding, in accordance with standard histopathological grading criteria for experimental BPH models. (Camara-Lopes et al. 2013).

Quantitative biochemical analysis of target proteins and signaling mediators (ELISA)

Concentration levels of nine crucial proteins and signaling mediators implicated in prostatic proliferation, inflammation, fibrosis, and androgenic activity were determined using high-sensitivity enzyme-linked immunosorbent assays (ELISAs) from BT LAB (China). All assays shared the same colorimetric principle; HRP conjugates facilitated the oxidation of the TMB substrate, which gives rise to a transient blue color. An acidic stop solution was then employed to terminate the reaction and turn the color into a stable yellow endpoint for subsequent measurements via spectrophotometry at 450 nm (Attarbashee et al. 2025b; Raheem et al. 2025). All readings were interpreted against a standard curve based on serial dilutions of known concentrations of each analyte, which permitted accurate quantifications across the physiological and pathological range (Luty et al. 2025a, 2025b; Motib and Idan 2025).

β-*Catenin (E1153Ra)*

β-Catenin, a crucial mediator of Wnt signaling and epithelial proliferation, was evaluated with the Aid of the Rat β-Catenin Sandwich ELISA kit (BT LAB, Cat. No. E1153Ra). Limit of sensitivity for the assay is 0.017 ng/mL. The prostate tissue supernatant was diluted afterward and allowed to react with immobilized capture antibodies followed by a biotinylated secondary antibody specific to β-catenin. Streptavidin–HRP conjugate was added for the color development, and absorbance was measured at 450 nm. This dual-antibody approach gave maximum specificity with regards to the target antigen, thus effectively blocking nonspecific binding and cross-reactivity.

Prostaglandin E2 (E0504Ra)

PGE2 was determined by the Rat PGE_2 Sandwich ELISA kit from BT LAB (Cat. No. E0504Ra), with a sensitivity of 0.026 ng per mL and span of work between 0.05 and 15 ng/mL. All tissue supernatants were processed by the homogenization method described in the protocol, and colorimetric changes proportional to PGE2 levels were read at 450 nm (Dawood and Abu-Raghif 2023; Sharif et al. 2026). Reliability in inflamed prostatic matrices made PGE2 assay robust for quantification.

Interleukin-27 (E0126Ra)

Interleukin-27 (IL-27) is a dual-function cytokine, assumed as both pro- and anti-inflammatory activities. Measurement of IL-27 was performed with the use of Rat IL-27 Sandwich ELISA kit (BT LAB, Cat. No. E0126Ra). The tissue lysate was first put in wells with specific antibody before detection by HRP-conjugated secondary antibody. The product of this reaction with TMB was a measurable yellow chromogen red at 450 nm (Yahiya et al. 2023; Shihab et al. 2025). This method provided a very sensitive analysis of cytokine involvement in the regulation of prostate immune signaling.

Interleukin-6 (E0135Ra)

IL-6 is a canonical marker for inflammation activation and was assessed using Interleukin Rat IL-6 Sandwich ELISA kit from BT LAB. The sensitivity of the assay was 0.052 ng/L with quantifiability limits at 0.1 ng/L to 40 ng/L. Tissue homogenates were on pre-coated plates and incubated successively with biotinylated detection antibodies and Streptavidin-HRP conjugate. Proportional color intensity was produced by this HRP-TMB reaction and read at 450 nm reflecting IL-6 activity in prostate microenvironment (Atarbashe and Abu-Raghif 2020; Abbas et al. 2022; AlBairmani et al. 2025).

Peroxisome proliferator-activated receptor-γ (e0284ra)

Peroxisome Proliferator-Activated Receptor-γ (PPAR-γ) is a nuclear receptor known for its metabolic regulation and anti-inflammatory functions; therefore, it was evaluated using BT LAB Rat PPAR-γ Sandwich ELISA kit (Cat. No. E0284Ra). A blue color generated by the HRP-TMB reaction turned yellow following acidification and was quantified at 450 nm (Aljawad et al. 2015). This was able to detect very sensitively the changes in PPAR-γ due to hormonal modulation in prostatic tissue.

Transforming growth factor -β (E0778Ra) and vascular endothelial growth factor (E0940Ra)

Transforming Growth Factor-β (TGF-β) and vascular endothelial growth factor (VEGF) were detected by ELISA using Rat TGF-β and VEGF Sandwich kit (BT LAB, Cat. No. E0778Ra, and E0940Ra respectively). After HRP catalysis of the TMB substrate, the resultant yellow color was measured at 450 nm. The absorbance had a direct relationship with tissue TGF-β and VEGF concentrations, further qualifying it to be an index of fibrotic and angiogenic activity in the prostate.

Proliferating cell nuclear antigen (E0398Ra)

Proliferating Cell Nuclear Antigen (PCNA), a nuclear marker of DNA replication and cell cycle events, was measured from the Rat PCNA ELISA kit (BT LAB, Cat. No. E0398Ra). The HRP-TMB colorimetric endpoint at 450 nm was representative of cellular proliferation strength. Measurements carried out by ELISA thus provided quantitative results that supplemented the histological analysis as a biochemical marker for epithelial hyperplasia.

Dihydrotestosterone (EA0046Ra)

Dihydrotestosterone (DHT), a potent androgen for prostate growth, was determined via a competitive inhibition ELISA kit (BT LAB, Cat. No. EA0046Ra). In this format, native DHT in the tissue homogenate competed with HRP-labeled DHT for antibody binding sites. Thus, the color intensity generated was inversely proportional to DHT concentration and was quantified at 450 nm. The specificity of the assay allowed for accurate determination of intraprostatic androgenic status.

Steroid 5α-reductase type 2 (E1585Ra)

Steroid 5α-reductase type 2, the key enzyme reducing testosterone to DHT, was measured from the BT LAB Rat 5α-reductase type 2 sandwich ELISA kit (Cat. No. E1585Ra). HRP catalyzed the oxidation of TMB by producing a stable yellow chromogen red at 450 nm. The absorbance magnitude thereby directly indicating enzyme abundance, hence reflecting androgenic enzymatic activity within prostatic tissues.

Molecular analyses of estrogen receptors

RNA extraction and quality assessment

Total RNA was extracted from rat prostate tissue using TransZol Up Plus RNA Kit, which includes chemical lysis followed by silica column purification. Both two steps provide high quality RNA that can be used for modern molecular assays. Initially, frozen prostate tissues were first powdered under liquid nitrogen to get the fine powder of tissue to completely rupture cells as well as preserve the integrity of RNA. Then the powdered tissue was homogenized with the aid of the TransZol Up reagent containing guanidine isothiocyanate, to denature proteins and inactivate the RNase that cause the degradation of RNA. After centrifugation, three separate parts-the organic phase, interphase and aqueous phase containing RNA-were formed. The upper aqueous phase contained RNA, collected, spun column-purified, and spectrophotometrically quantified to confirm suitability for complementary DNA (cDNA) synthesis and quantitative PCR (qPCR) analysis (Shareef et al. 2025).

cDNA generation

Isolated RNA was converted into complementary DNA (cDNA) through the EasyScript First Strand cDNA Synthesis SuperMix which consists of reverse transcriptase, ribonuclease inhibitors and random primers to ensure high efficiency and reproducibility. Reverse transcription was performed in three steps including primer annealing at 25 °C for 11 minutes, followed by cDNA synthesis at 41 °C for 35 min, and then enzymatic deactivation at 85 °C for 5 min. Thus, complete conversion of mRNA into stable cDNA templates for use in downstream amplification was assured.

Design of primers and conditions of amplification

For the amplification of estrogen receptor beta (ERβ) transcripts, gene-specific primers were designed. The gene-specific primers employed were: forward 5'-TGAACAACCTGAAGCGGAGT-3' and reverse 5'-CAGGGATCCAGTCTCGGTGT-3'. Lyophilized primers were reconstituted at 100 pmol/μL and adjusted to 10 pmol/μL for use. Quantitative PCR was carried out based on a typical thermal cycling procedure; prior activation of the polymerase and full denaturation of double-stranded DNA at 95 °C for 10 minutes constituted the first step. In the subsequent steps, the 40 activation cycles comprised decompression at 95 °C for 20 seconds, roasting at 55 °C for 20 seconds, followed by elongation at 72 °C for 20 seconds. The annealing temperature was optimized according to the Tm of the primers used for specific and efficient amplification.

Quantitative analysis on gene expression relative amount of mRNA

ERβ was quantified using the ΔΔCT (2–ΔΔCT) method, which is comparative normalizing against an internal reference gene. The cycle threshold (CT) values of ERβ of all samples were first standardized to the housekeeping gene, which is generating a ΔCT value for all the variations in the RNA input and efficiency of reverse transcription. Then experimental group ΔCT values were compared with the control group, obtaining ΔΔCT values. Thus, 2–ΔΔCT calculates fold change in expression; values more than one indicate upregulation, whereas values less than one indicate downregulation relative to controls (Saleh and Motib 2023).

Immuno-histochemical analysis of BCL2

The anti-apoptotic protein BCL2 was detected using immunohistochemistry on paraffin-embedded prostate tissue samples. Portions were paraffin-treated in xylene, moisturized with successive ethanol concentrations, and heated to enable antigen extraction, which was performed in a buffer comprising citrate (pH 6.0). Endogenous peroxidase capacity was inhibited with 3% hydrogen peroxide, whereas background random attachment was blocked using 5% ordinary goat serum. The slides were then treated nightly at 4 °C with a monoclonal anti-BCL2 antibody (R&D Systems, USA, Cat. No. MAB8272) diluted to a working concentration of 8–25 µg/mL. The Dako EnVision FLEX polymer system (Dako, Denmark) was utilized for detection and this employs an HRP-labeled secondary polymer complex that is devoid of biotin for less background staining.

Chromogenic visualization with the EnVision FLEX DAB+ Chromogen yields localized brown precipitate at antigen sites reacting with HRP. Counterstain with Harris Hematoxylin is employed to delimit nuclear morphology. Slides were finally dehydrated, cleared, and mounted with the DPX medium. Processed sections were investigated under brightfield microscope to assess the spatial distribution and intensity of BCL2 expression within epithelial and stromal compartments. Quantitative analysis of the immunostained tissue sections was performed using ImageJ software equipped with an immunohistochemistry (IHC) analysis plug in, which allows for the determination of exact staining intensity and distribution.

Statistical analysis

All quantitative data were studied for normality utilizing applicable statistical tests before they were analyzed. Parametric data were analyzed using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison test to determine intragroup differences. Nonparametric data were analyzed by the Kruskal-Wallis test, and if they showed significance, Dunn's post hoc test was used. Mean ± standard deviation (Mean ± SD) was the expression of data. Statistical significance was considered at $p < 0.05$. All analyses were accomplished using GraphPad Prism (version 9.0; Boston, MA, USA).

Results

Prostate weight and prostate index

The administration of testosterone (TEST) led to a significant and statistically convincing enlargement of the prostate gland compared to that of the Normal control (N) group (P<0.0001). This increase in organ mass indicates an obvious induction of androgen-driven prostatic hypertrophy. In consideration of opposing this abnormal growth, treatment with finasteride (TEST+FINA), a 5α-reductase inhibitor, produced a robust reduction, bringing the weight of the prostate back to the level of the control baseline (P<0.0001 vs TEST) (Fig. 1a). Compared to finasteride, dinoprostone (TEST+DINO) has shown similar results leading to an equally significant reduction in prostate weight (P<0.0001 vs TEST). Notably, the final organ weights obtained in both treatment groups were statistically indistinguishable, indicating parallel therapeutic outcomes against testosterone-induced hypertrophy (Fig. 1a).

A parallel pattern was observed in the prostate index, which normalizes organ weight with respect to body weight. The TEST group showed a tremendous, statistically significant rise in this index (P<0.0001 vs N), thus confirming the existence of hypertrophic pathology (Fig. 1b). Both TEST+FINA and TEST+DINO treatments reversed this aberration, yielding results statistically comparable to those seen in the N group. The suppression of index elevation by both interventions was highly significant (P<0.0001 vs TEST), and no intergroup difference was found between finasteride and dinoprostone, lending weight to their similar strength in restraining androgen-mediated growth responses (Fig. 1b).

Histopathology score and proliferative marker

The prostates of the TEST group exhibited severe glandular hyperplasia characterized by epithelial stratification, increased luminal folding, and stromal expansion. Semi-quantitative scores exhibited a highly substantial increment in the histopathology grade in the TEST group as matched to the N group (P<0.0001), suggestive of diffuse proliferative changes (Fig. 2a and 2c). Treatment with either finasteride or dinoprostone had a remarkable amelioration of these microscopic changes, with both having statistically comparable median scores (≈1.5; P<0.0001 vs TEST). Restoration of glandular architecture, reduction in epithelial crowding, and normalization of acinar morphology reflect strong antihypertrophic activities of both agents, without significant differences between agents (Fig. 2a, c).

PCNA, a key indicator of cellular replication, was remarkably overexpressed in the TEST group (P< 0.0001 vs N), confirming hyperproliferative phenotype. Treatment with either finasteride or dinoprostone, significantly reduced PCNA expression (P<0.0001 vs TEST), to nearly N baseline levels. Since two treatments did not differ significantly from each other, it indicates that both treatments are equally effective in curbing cellular proliferation within the prostatic tissue (Fig. 2b).

Androgen metabolism and proliferative signaling cascade

Dihydrotestosterone (DHT) and 5α-reductase type 2 activity

The androgen metabolism is absolutely dysregulated in the testosterone-induced hypertrophic model through

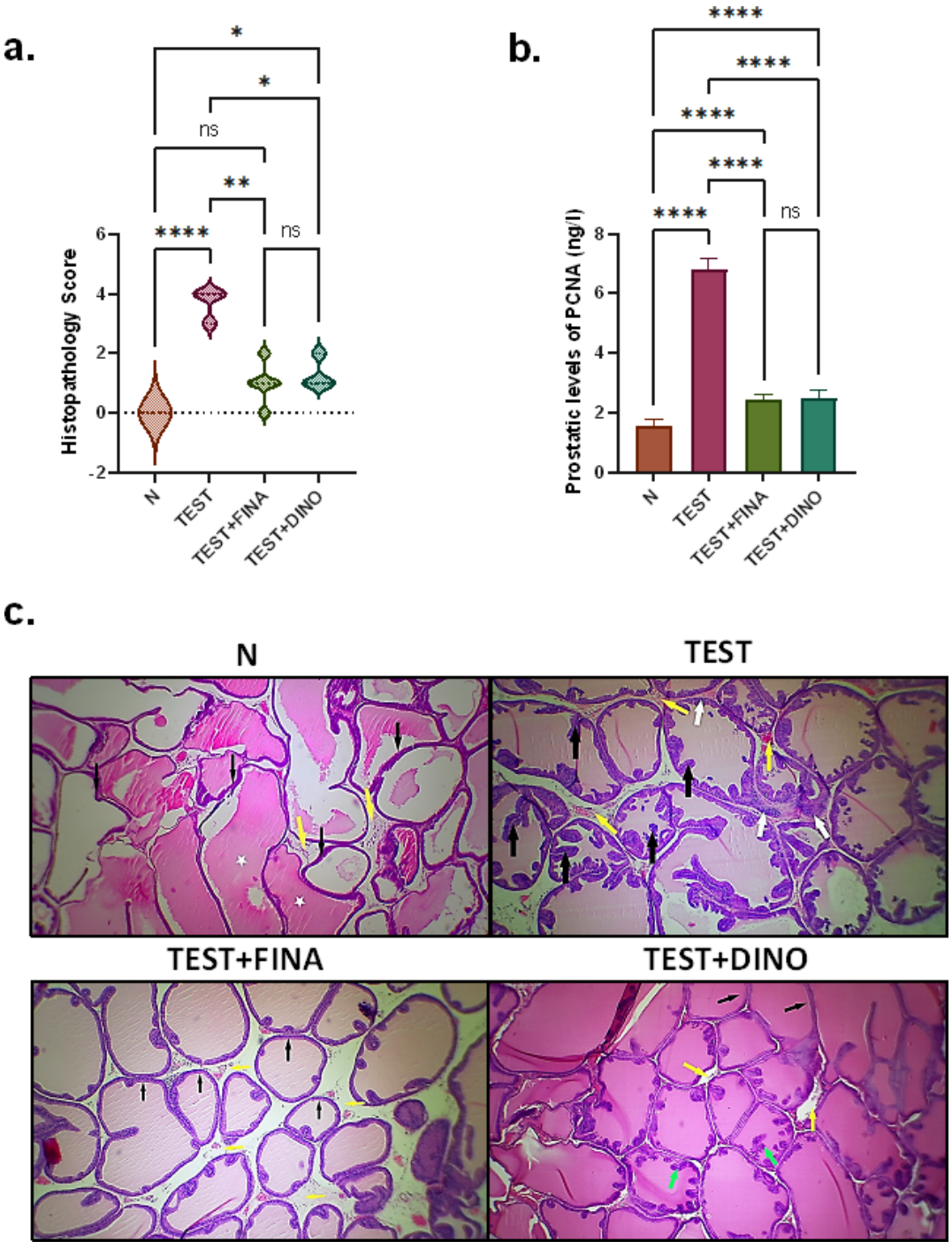

Figure 1. Effects of Treatments on Prostate Weight and Prostatic Index. This figure illustrates the effects of different kinds of drugs on various prostate size parameters. Mean prostate weight (mg) is shown in Panel (**a**), and Prostatic Index (mg/g) in Panel (**b**). TEST administration results in a highly significant increase in both prostate weight and prostatic index as compared to normal controls (N) ($p < 0.0001$), thus confirming the successful induction of prostatic hypertrophy. Co-treatment with either finasteride or dinoprostone successfully prevented these testosterone-induced increases. In both treatment groups, prostate weight and index values were remarkably lower, approaching those of the normal group, and there was no statistically significant difference between the latter two treatments. Panel (**c**) shows representative photomicrographs of 400× magnification with H&E staining correlating with the aforementioned scores. The N group represents normal glandular acini and profuse luminal secretion (white stars). The TEST group displays frank signs of BPH with epithelial hyperplasia with stratification (white arrows) and papillary projections against a backdrop of dense fibromuscular stroma (yellow arrows). Treatments TEST+FINA and TEST+DINO were both found to alleviate this hyperplastic condition. Interestingly, the TEST+DINO group exhibited a marked reduction of epithelial height and stratification (green arrows), returning a morphology that more closely resembles the normal condition, hence supporting its potent action in reducing testosterone-induced prostatic proliferation and hyperplasia. Data are reflected as mean ± SD, where * represents $P<0.05$, ** $P<0.01$, *** $P<0.001$, and **** $P<0.0001$; "ns" indicates not significant or no difference (n= 10). Group abbreviations are as follows: N, Normal control; TEST, Testosterone-treated group; FINA, Finasteride; DINO, Dinoprostone.

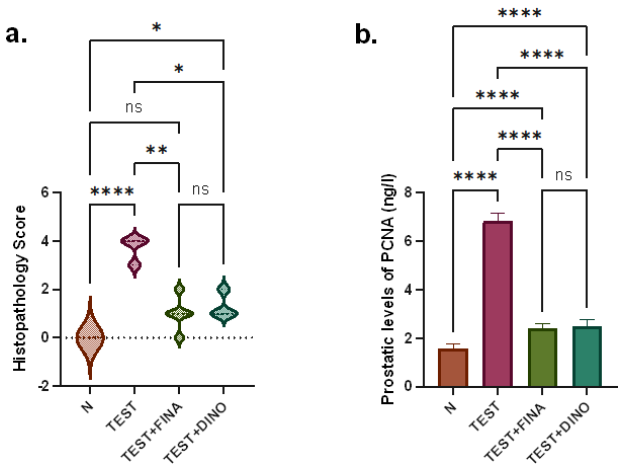

Figure 2. Histopathology Score and Prostatic Levels of PCNA. **a.** Histopathology Score: Testosterone (TEST) treatment produced a remarkable rise in the histopathology score opposed to the normal controls (N), indicating marked prostatic tissue alterations characteristic of hyperplasia. Co-administration of finasteride (TEST+FINA) or dinoprostone (TEST+DINO) effectively reduced this elevation. **b.** Prostatic PCNA Levels: PCNA expressions were considerably upregulated in the prostates of the TEST group, reflecting enhanced cellular proliferation. Treatment with finasteride or dinoprostone significantly suppressed this rise, normalizing PCNA levels close to those of the control group. Data are reflected as mean ± SD, where * denotes P<0.05, ** denotes P<0.01, *** denotes P<0.001, and **** denotes P<0.0001; "ns" indicates no significant difference (n= 10). Group abbreviations are as follows: N, Normal control; TEST, Testosterone-treated group; FINA, Finasteride; DINO, Dinoprostone.

the significant elevation of intraprostatic levels of DHT concentrations (P<0.0001 vs N). This potent androgen is produced by the catalytic activity of 5α-reductase type 2, which makes a central contribution to stimulating cellular multiplication in the prostatic epithelium and stroma. Finasteride treatment (TEST+FINA) is known to have this effect, as it significantly reduces DHT accumulation (P<0.0001 vs TEST). Dinoprostone (TEST+DINO) also produced an impressive result, reaching statistical significance in reducing DHT levels (P<0.0001 vs TEST), suggesting a potential role for this drug in modulating androgenic signaling indirectly. In contrast, finasteride had a slightly greater effect on DHT suppression (P<0.05 vs TEST+DINO), in keeping with its specificity for the enzyme target (Fig. 3a).

Concurrently, testosterone has increased 5α-reductase activity (P<0.0001 vs N), supporting the biochemical amplification of DHT production in the area. Both the TEST+FINA and the TEST+DINO groups had significant inhibition of this enzyme activity (P<0.0001 vs TEST), with levels comparable to those of normal. The lack of any major disparities between the two therapeutic groups implies that dinoprostone does indeed have a magnitude of action on androgen metabolism comparable to that of finasteride (Fig. 3b).

β-Catenin signaling

Validation of β-catenin, a key effector of the canonical Wnt signaling cascade, and a major important regulator of circuits for proliferation and differentiation within cells, was markedly regulated in the TEST group (P<0.0001 vs N). This threshold reveals a proliferative signaling environment active within the hypertrophied prostate. Both treatments were able to repress β-catenin accumulation (P<0.0001 vs TEST), and a mildly stronger offer was obtained among finasteride regarding exerting a suppressive effect compared to dinoprostone (P<0.05). These data invoke β-Catenin modulation as a convergent downstream target for androgenic and prostaglandin-mediated signals (Fig. 3c).

Estrogen receptors β

ERβ gene expression was increased dramatically in the TEST group: nearly eight-fold that of N (P<0.0001). This gene has been known to mediate prostatic growth and differentiation by crosstalk with androgenic mechanisms. Both finasteride and dinoprostone inhibited ERβ expression (P<0.0001 vs TEST), but finasteride resulted in a statistically greater reduction. This indicates that while both agents restore hormonal receptor homeostasis, finasteride demonstrates a stronger modulatory capacity over estrogenic signaling components (Fig. 3d).

Pro-inflammatory cytokines (IL–6 and PGE_2)

Aspects of inflammation were quite pronounced in the testosterone-treated group, as illustrated by a remarkable increment in the cytokine IL–6 (P<0.0001 vs N). Finasteride and dinoprostone both significantly reduced this inflammatory peak (P<0.0001 vs TEST), but indeed, finasteride imparts a more significant decrease in IL–6 itself (P<0.05) (Fig. 4a). Toughly the same, prostatic prostaglandin E_2 (PGE_2) showed higher levels in the testosterone-treated group compared to normal (P<0.0001 vs N), thus indicating activation of inflammatory and prostanoid signaling. Both treatments normalized PGE_2 levels (P<0.0001 vs TEST), with finasteride showing again a higher efficacy (P<0.001 vs T+DINO), suggesting its dual anti-androgenic and anti-inflammatory benefit (Fig. 4b).

Growth factors (TGF-β and VEGF)

Statistically significant increases in TGF–β were noted in the TEST group, important for fibrotic remodeling and epithelial–mesenchymal transition (P<0.0001 vs N). Both treatments produced comparable and highly statistically significant suppression of TGF–β expression (P<0.0001 vs TEST), restoring near-physiological levels without any inter-group variation (Fig. 4c). VEGF, a marker of prostatic angiogenesis and tissue remodeling, was increased greatly by testosterone application (P<0.0001 vs N). Both ther-

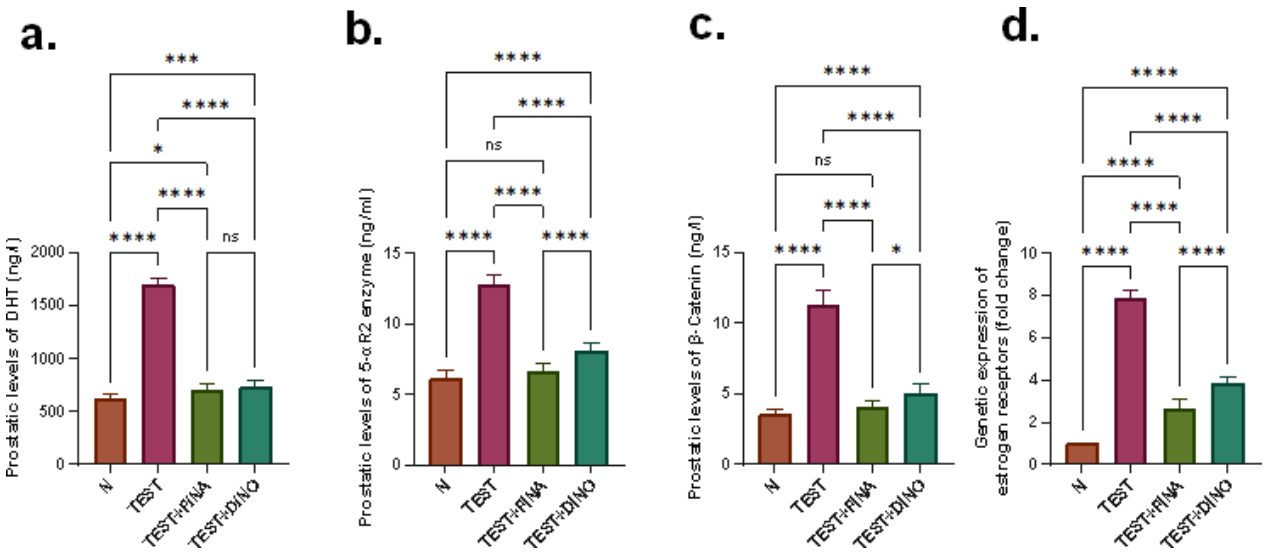

Figure 3. Prostatic levels of DHT, 5–αR2 enzyme, β-Catenin, and genetic expression of estrogen receptors. **a.** The DHT levels elevated in the prostate: TEST treatment markedly elevated the levels of prostatic DHT when compared to the Normal (N) group, verifying increased androgenic activity. Both finasteride treatment (TEST + FINA) and dinoprostone treatment (TEST + DINO) conspicuously inhibited this elevation, with finasteride causing a much greater attenuation than dinoprostone. **b.** 5α- reductase enzyme levels in the prostate: The TEST significantly stimulated the activity of the 5α-reductase enzyme when compared to the Normal group while both treatments equally diminished this increase. **c.** Prostatic β-Catenin levels: TEST caused an increase in β-Catenin much more than did N, while both TEST+FINA and TEST+DINO significantly reversed the elevation to a larger extent, with finasteride being more effective than dinoprostone. **d.** Genetic expression of estrogen receptors: TEST produced a significant upregulation of the estrogen receptor genetic expression compared to the N group; both TEST+FINA and TEST+DINO counteracted this induction to variable extents, with finasteride being relatively the most effective. Data are reflected as mean ± SD, where * denotes P<0.05, ** denotes P<0.01, *** denotes P<0.001, and **** denotes P<0.0001. Group abbreviations are as follows: N, Normal control; TEST, Testosterone-treated group; FINA, Finasteride; DINO, Dinoprostone.

apy protocols delivered strong anti-angiogenic efficacy (P<0.0001 vs TEST), but the level of VEGF inhibition was statistically indistinguishable between the two (Fig. 4d).

Regulatory cytokines and cell fate markers (IL–27, PPAR–γ, and BCL2)

The regulatory cytokine IL–27, involved in immune modulation and chronic inflammatory signaling, was markedly elevated in the TEST group (P<0.0001 vs N). Both treatments significantly suppressed IL-27 expression (P<0.0001 vs TEST), with finasteride causing slightly stronger suppression (P<0.05 vs TEST+DINO) (Fig. 4e).

Among the nuclear receptors controlling cellular differentiation and growth, peroxisome proliferator-activated receptor-γ (PPAR–γ) was largely downgraded in the TEST group (P<0.0001 vs N). Both treatments likewise elevated PPAR–γ levels significantly back toward its baseline (P<0.0001 vs TEST) in effect mapping the reactivation of anti-proliferative and metabolic homeostatic pathways. No significant difference between finasteride and dinoprostone was recorded regarding this reparation (Fig. 4f).

The transcription of BCL2, the anti-apoptotic protein, was hoisted to greater levels due to testosterone (P<0.0001 vs N), which means activation of the survival pathway in the cells. Interestingly, finasteride and dinoprostone were able to further increase BCL2 expression (P<0.05 and P<0.01 vs TEST respectively). This supports the idea that the action of either finasteride or dinoprostone may be exerted through a cytostatic, not pro-apoptotic mechanism, in the context of androgen withdrawal (Fig. 4g and 4h).

Discussion

BPH has become an increasing health threat characterized by an age-related, nonmalignant proliferation affecting both glandular-epithelial and stromal components of the prostate (Hata et al. 2023). The pathomechanism of BPH encompasses a unique interconnection of hormonal changes, age-dependent tissue remodeling, and chronic low-grade inflammation, which work additively or synergistically to induce hyperplastic change and tissue remodeling (Alshahrani 2025). Current pharmacotherapeutic options mainly include α-adrenergic receptor antagonists targeting the dynamic component and 5-ARIs targeting the static component. Such treatments, although providing some symptomatic relief, usually have adverse endocrine and sexual side effects that compromise patient adherence over extended periods. Hence, the need for novel mechanism-based therapeutics that can better modulate prostatic growth and function with an improved safety and tolerability profile.

Dinoprostone administration afforded complete pharmacological reversal of testosterone-induced prostatic hypertrophy, as evidenced by normalization of prostate size,

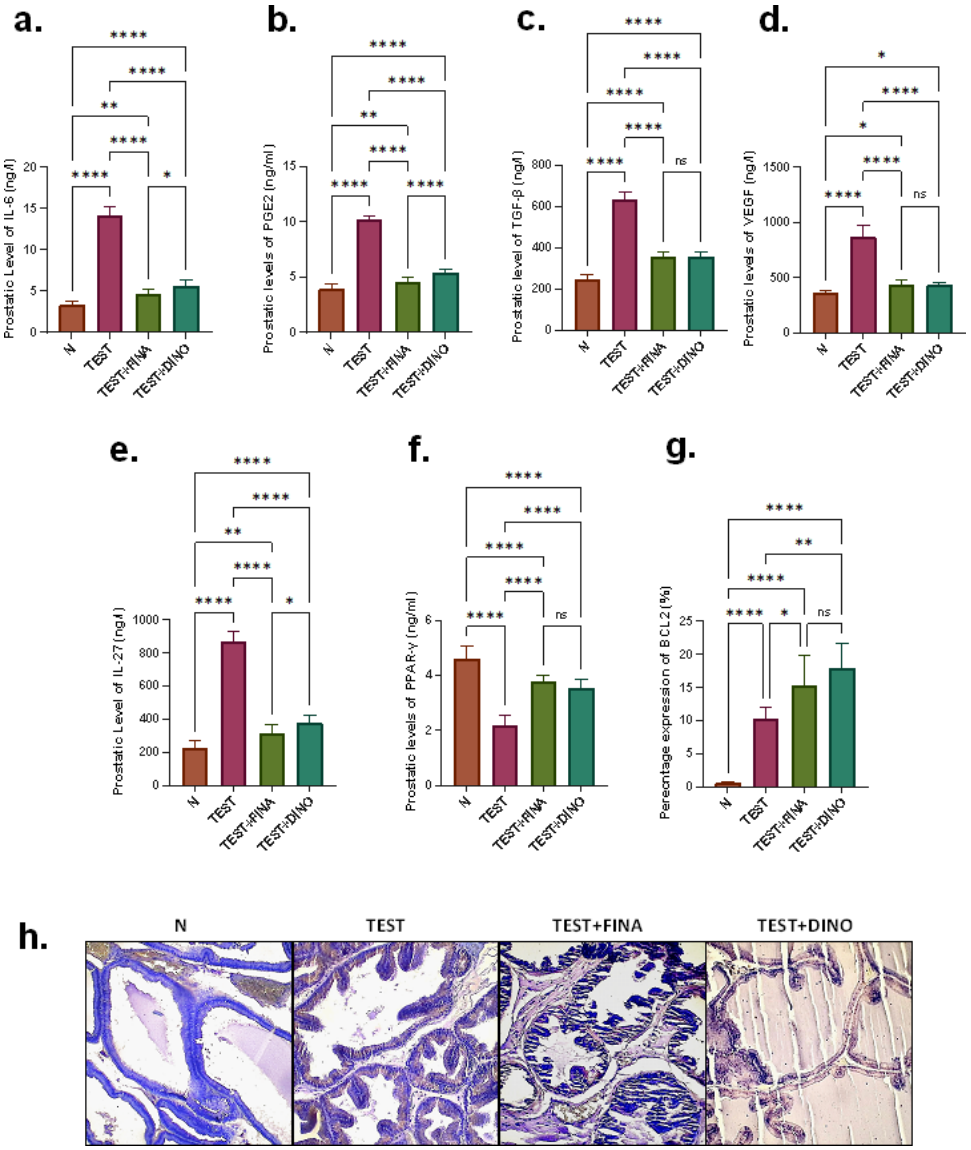

Figure 4. Prostatic levels of IL-6, PGE_2, TGF–β, VEGF, IL–27, PPAR–γ and percentage expression of BCL2. **a.** Prostatic IL–6 levels: Testosterone (TEST) administration sharply upregulated levels of IL–6 compared to the Normal (N), indicating marked pro-inflammatory reactivity. Both Finasteride (TEST+FINA) and dinoprostone (TEST+DINO) downregulated this increase significantly, but the effect of finasteride is greater than that of dinoprostone ($P < 0.05$). **b.** Prostatic levels of PGE_2: TEST treatment significantly increased PGE_2 levels concerning the normal group, indicating an enhancement of prostaglandin synthesis. Both TEST+FINA and TEST+DINO were effective in downregulating this increase, with finasteride giving even greater attenuation as compared with dinoprostone ($P<0.01$). **c.** Prostatic levels of TGF–β: TEST treatment significantly increases the level of TGF–β compared to N, indicating fibrotic activation. Both finasteride and dinoprostone treatments considerably prevented such elevation and brought values toward those related to normal baselines, with no significant difference detected within these two groups at that time. **d.** Prostatic level of VEGF: VEGF levels in the TEST group were greatly enhanced over those of N, where both suggest increases in angiogenic activity. Both TEST+FINA and TEST+DINO effectively reduced VEGF expression, and their efficacy was comparable without a significant difference. **e.** Prostate level IL –27: TEST increased its levels of the IL–27 dramatically compared with N, which would support a more increased inflammatory activity. Both TEST+FINA and TEST+DINO lowered the levels of IL–27 substantially, whereas finasteride elicited a greater reduction compared with that of dinoprostone ($P<0.05$). **f.** Prostatic level of PPAR–γ: TEST treatment significantly lowered PPAR–γ levels in comparison to N, indicating that this anti-inflammatory nuclear receptor is down-regulated. Finasteride as well as dinoprostone treatments significantly restored PPAR–γ levels towards normal values, while there were no significant differences between the two interventions. **g.** BCL2 percentage expression: TEST caused a marked rise in the production of BCL2 when opposed to N, denoting the increase in anti-apoptotic signaling. Interestingly, treatment with finasteride caused a further increase that was statistically significant compared to both N and TEST groups ($P<0.0001$ and $P<0.01$, respectively). Dinoprostone also raised BCL2 compared to normal, but this effect was not significantly different from TEST. **h.** Representative photomicrographs (400×) of immunostained prostatic sections. Data are reflected as mean ± SD, where * stands for $P<0.05$, ** for $P<0.01$, *** for $P<0.001$, and **** for $P<0.0001$, while "ns" implies no substantial change (n=10). Group abbreviations: N, Normal control; TEST, testosterone-treated group; FINA, Finasteride; DINO, Dinoprostone.

prostatic index, and microscopic architecture. This finding directly contradicts the prevailing postulates that link PGE2 signaling to enhanced cellular proliferation, survival, migration, and angiogenesis in proliferative disorders, including prostate cancer (PCa) (Zhang and Daaka 2011; Nakanishi and Rosenberg 2013; Dufour et al. 2014; Madrigal-Martínez et al. 2018; Finetti et al. 2023; El-Sehrawy et al. 2025). In prostate cancer models, elevated PGE2, primarily through EP2 and EP4 receptors, stimulates growth-promoting cascades through the mechanisms of cAMP and Phosphoinositide 3-kinase (PI3K)/Akt signaling (Fujino et al. 2003; Fukushima et al. 2022; Abdul-Majeed et al. 2025). Therefore, it's plausible that the observed anti-hypertrophic effects shown in the current BPH model require a novel, context-dependent regulatory mechanism either preceding or antagonizing the canonical EP2 pro-proliferative function.

Increased expression of PCNA is a hallmark of DNA synthesis and G1/S phase increase, and it is significantly increased in hyperplastic prostate tissue (Strzalka and Ziemienowicz 2011). Administration of dinoprostone caused a profound downregulation of PCNA, thus confirming its strong anti-proliferative potential. This downregulation might be an effect of concomitant suppression of androgenic stimulation and direct manipulation through the EP2/cAMP signalling (Sharquie et al. 2005; Weinberg et al. 2009). The cAMP/PKA signaling generally supports growth of epithelial cancers (Zhang et al. 2020b), while in non-malignant or relatively early hyperplastic conditions, increased cAMP/PKA activity may induce regulatory kinases enacting cell cycle arrest (Zhang et al. 2020a).

The literature evidences the mechanistic complexity of PGE2 signaling. While PGE2 promotes proliferation through EP2 activation in PC3 prostate cancer cells, thereby enhancing its growth-supporting profile, the contradicting observations witnessed in non-prostatic model systems have put into question the universality of this paradigm. For example, EP2 activation inhibits mitogenesis in PDGF-activated rat hepatic stellate cells (Koide et al. 2004), which raises the possibility of cAMP-mediated signaling being an anti-proliferative regulatory pathway in specific non-malignant settings. Therefore, the association of PCNA with tumor progression further supports the relevance of PCNA as a pathological marker in prostatic cancer.

PGE_2 signaling demonstrates a marked context-dependent biological outcome that is influenced by receptor subtype activation (EP1–EP4), tissue microenvironment, and disease state (Matsuoka and Narumiya 2007; Wang et al. 2025). Although PGE_2 is largely recognized to drive proliferation and tumor progression in prostate cancer, its effects on non-malignant hyperplastic tissue may be vastly different (Mizuno et al. 2019; Finetti et al. 2020; Cheng et al. 2021). PGE_2 signaling in benign prostatic hyperplasia may modulate inflammation, cellular growth control, and pathways dependent on androgen (De Nunzio et al. 2016; Jin et al. 2021). These distinct effects are likely mediated by selective engagement of EP receptor subtypes and downstream intracellular signaling pathways (Tsuge et al. 2019; Kimuro et al. 2025). Consequently, the anti-proliferative and protective effects seen in our current study may be a function of receptor-specific signaling dynamics that differ from classical tumor-promoting modes of action generally ascribed to PGE_2 delivery in malignant prostate models (Tian et al. 2008; Wada et al. 2015; Song et al. 2016).

Dihydrotestosterone, the main androgen that stimulates prostatic growth in BPH, is produced from androgen testosterone by steroid 5α-reductase type 2. Finasteride acts by inhibiting 5α-reductase to curtail DHT production and halt the progression of BPH (Thomas et al. 2008). In an interesting twist, dinoprostone-an eicosanoid with effects and structure different from 5-ARIs-has emerged as an in vivo interesting candidate for inhibiting both 5α-reductase activity and intraprostatic DHT levels.

β-Catenin is a key regulator of Wnt signals, promotes proliferation via TCF/LEF transcription and cooperates with the Androgen Receptor (AR) (Truica et al. 2000; Pakula et al. 2017). The inhibition of β-Catenin by dinoprostone indicates that an intersection exists among androgenic and prostaglandin-mediated types of signaling. The downregulation of β-Catenin could, possibly, be due to a decrease in DHT levels, which prevents AR-induced transcriptional activation (Terry et al. 2006; Lee et al. 2015). PGE2/EP2 generally stabilizes β-Catenin in malignant settings such as colon cancer through cAMP/PKA (O'Callaghan and Houston 2015), whereas in this BPH context, it seems that such signal may act in the other distant direction.

ERβ expression was significantly upregulated in testosterone-induced BPH, indicating some degree of hormonal dysregulation. Although dinoprostone does not bind directly to estrogen receptors, mounting evidence suggests that PGE2 may interfere with cellular processes associated with estrogen signaling through different intracellular pathways (Monsivais et al. 2014; Kim et al. 2017; Shah and Kazi 2022). The indirect regulatory effects elaborated in the cases of cancer and endometriosis demonstrate a fine interplay between the signaling networks of prostaglandins and estrogens.

Transforming Growth Factor-β (TGF-β) is a multipurpose cytokine that has fibrogenic and proliferative activity (Kadhim et al. 2022). TGF-β generally assembles the master regulator of tissue fibrosis and stromal thickening, which are the major contributors to static obstruction in BPH. According to the research, dinoprostone inhibits TGF-β significantly compared to finasteride. The activity of anti-fibrotics would most likely be related to EP2/cAMP signaling, where PKA suppresses canonical Smad signaling by inhibitory phosphorylation of Smad2/3, thus preventing fibrosis gene transcription (Kolodsick et al. 2003; Yang et al. 2014). This is reinforced by dermal fibrosis models in which PGE2 through EP2 can inhibit TGF-β1-induced collagen synthesis (Zhao et al. 2016).

VEGF is a critical modifier of angiogenesis, controlling vascular growth and tissue remodeling (Khaleel et al. 2025b; Khaleel et al. 2025a; Thammer et al. 2025).

In BPH, raised VEGF levels encourage prostatic vascularization and epithelial hyperplasia, thereby supporting gland enlargement. Dinoprostone, on the other hand, has been found to reduce the expression of VEGF significantly, which is quite contradictory according to the notion that EP2 promotes angiogenic actions. This inhibition also likely reflects the dominance of the anti-androgenic signaling system since DHT strongly induces the transcription of VEGF (Häggström et al. 2002; Sieveking et al. 2010; Cai et al. 2011). Thus, the DHT reduction leads to a downstream inhibition of VEGF expression by dinoprostone, proving EP2's predominant role as an effector of angiogenic signaling in the BPH microenvironment.

Chronic inflammation with increased IL-6 and PGE2 is pivotal in the BPH development process. Dinoprostone and finasteride reduced IL-6 and normalized intraprostatic PGE2. Changes in PGE2 levels indicate a kind of negative feedback mechanism with exogenous dinoprostone occupancy of the EP receptors downregulating COX-2 and mPGES-1 expression (Sood et al. 2014). Inhibitory effects on the nuclear translocation of NF-κB, plus reduced androgenic drive (Hong et al. 2010; Culig 2021), seem to underline IL-6 suppression through EP2/cAMP signaling.

Dinoprostone also inhibited IL-27, the cytokine which is a part of chronic inflammation, as suggested by the fact that PGE2 signaling prevents the production of IL-27, which indicates that dinoprostone is shifting the prostate away from a Th1-dominant inflammation state (Hooper et al. 2017). Although IL-27 can behave as an anti-tumor cytokine, the reduction of it is mainly given by the decrease of chronic inflammation in this case.

Dinoprostone remarkably restored PPAR-γ expression, a nuclear receptor often downregulated during BPH and having anti-inflammatory and anti-proliferative actions. Induction of the EP2/cAMP/PKA cascade may facilitate increased transcription or stability of PPAR-γ to reverse testosterone-induced suppression and restore the important homeostasis checkpoints required for metabolism and differentiation (Kim et al. 2010; Jiang and Dingledine 2013).

Both dinoprostone and finasteride increased the level of the anti-apoptotic protein BCL2 in BPH tissues. Although BCL2 overexpression is associated with tumor survival, it sometimes is linked with the powerful inhibition of proliferation (decreased PCNA), which indicates a change toward cytostasis rather than hyperplasia. Dinoprostone decouples prosurvival activity and proliferation through EP2/cAMP/PKA signaling (Vassiliou et al. 2004; George et al. 2007; Kitase et al. 2010), maintaining tissue viability while halting growth. This cytostatic equilibrium is opposed to a risk for the long-term safety benefits involved compared with extensive apoptosis-driven treatments because it minimizes apoptotic tissue loss.

Study limitations

This study has certain limitations. First, a single dose of dinoprostone was studied, and dose-response relationships could thus not be determined. Second, the experimental design lacked a vehicle-only control group as a comparison for potential confounding effects of the solvent system employed to dissolve dinoprostone, potentially precluding complete exclusion of such vehicles. Lastly, the results are derived from a short-term rodent model of testosterone-evoked prostatic hyperplasia and do not offer any long-term safety or efficacy data. Further validation will be required in future studies to verify these findings, including multiple dosing regimens, longer treatment periods, and dedicated vehicle controls.

Conclusion

Dinoprostone may serve as a potent agent in the experimental reversal of BPH. It has shown comprehensive anti-proliferative, anti-fibrotic, and anti-inflammatory effects like those of finasteride. Its mechanism of action is new and context-dependent, defined by strong indirect inhibition of the 5α-reductase/DHT axis combined with an EP2-mediated decrease in stromal structural remodeling factors such as TGF-β. Resolution of the PGE2 paradox lies, instead, in inducing a cytostatic state of quiescent survival, characterized by cell proliferation suppression (decreased PCNA) but increased viability (increased BCL2). The results thus validate the EP2 receptor as a good pharmacological target for not only BPH symptomatology but also structural disease modification, in that it offers smooth muscle relaxation among the benefits. Develop future drugs focusing on the selective EP2 modulators that keep preferentially defined inhibitory pathways active and will have strong cross-talks with the actors of 5-ARIs (i.e., anti-TGF-β, cytostatic, anti-inflammatory effects).

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

Experiments on animals: The study was approved by the Institutional Review Board (IRB) and the Institutional Animal Care and Use Committee (IACUC) of Al-Nahrain University (Approval No.: IRB/20250025), and all treatments were performed in accordance with the guidelines established by the NIH Guide for Care and Use of Laboratory Animals.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Artificial Intelligence (AI) use

The authors accept full responsibility for the content of the manuscript, including the disclosure of any use of AI.
No AI tools were used in the preparation of this manuscript.

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Author contributions

Ahmed Khalid Aldhalmi conducted the research and collected data, contributed to the conception and planning of the study, and prepared the first draft of the manuscript. Bahaa Abdul-Hussein contributed to the revision, experimental design, statistical analysis, and data interpretation. Israa Kadhim Mejbel Mashloosh contributed to the revision, resources, data collection, experimental design, and statistical evaluation. Hayder Ridha-Salman finalized the manuscript and contributed to the methodology, programming, and statistical analysis.

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Data availability

Data validating the findings of this present research are obtainable from the corresponding author upon reasonable request.

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