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Ethanol Extract of *Cosmos caudatus* Attenuates Oxidative Stress and Inflammation in a Testosterone-Induced Benign Prostatic Hyperplasia Rat Model via Reduction of Malondialdehyde, Interleukin-6, and Tumor-Infiltrating Lymphocytes Activity

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ABSTRACT

Benign Prostatic Hyperplasia (BPH) is a common age-related urological condition driven by chronic inflammation and oxidative stress, prompting the search for safer phytotherapeutic alternatives. This study evaluated the in vivo efficacy of ethanolic extract of *Cosmos caudatus* leaves in modulating the oxidative-inflammatory axis underlying testosterone-induced benign prostatic hyperplasia. Blood samples (0.5–1 mL) were collected from the retro-orbital plexus at baseline (T0), post-induction (T1), and post-treatment (T2) of thirty male *Rattus norvegicus* obtained from the Laboratory Animal Unit, Universitas Sebelas Maret, were allocated into five groups (n=6): Normal, Control, Positive Control receiving Finasteride, and treatment groups administered C. caudatus extract at 125 mg/kg or 250 mg/kg. BPH was induced using testosterone propionate (3 mg/kg/day, s.c.) for 28 days, followed by a 28-day treatment period. Serum malondialdehyde, interleukin-6, stromal tumor-infiltrating lymphocytes, prostate weight, and prostate index were evaluated. Testosterone induction significantly increased oxidative stress, systemic inflammation, and stromal lymphocytic infiltration, together with notable prostate enlargement ($p<0.05$). Treatment with both doses of *C. caudatus* extract markedly reduced malondialdehyde and interleukin-6 levels, suppressed tumor-infiltrating lymphocytes infiltration, and decreased prostate weight and prostate index compared with the untreated benign prostatic hyperplasia group ($p<0.05$), showing therapeutic effects comparable to Finasteride. These findings demonstrate that *C. caudatus* effectively attenuates benign prostatic hyperplasia progression through strong antioxidant and anti-inflammatory mechanisms, indicating its potential as a promising phytotherapeutic candidate targeting the oxidative-inflammatory axis in benign prostatic hyperplasia.

Keywords: Benign Prostatic Hyperplasia, Cosmos caudatus, Oxidative Stress, Inflammation.

Introduction

Benign Prostatic Hyperplasia (BPH) is a chronic, degenerative condition representing one of the most prevalent urological diseases in aging men globally. Its prevalence increases starkly with age, rising from 8% in the fourth decade of life to 80% by the ninth decade.[1] This high prevalence translates into a significant and growing global health burden, with both the incidence and morbidity of BPH doubling between 1990 and 2019.[2,3] The disease progressively impairs quality of life through Lower Urinary Tract Symptoms (LUTS) and can lead to severe complications, including acute urinary retention, recurrent infections, and renal dysfunction.[4]

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Current standard therapies, while effective for many, are constrained by significant limitations. Surgical intervention (TURP) carries a notable risk of complications and re-intervention.[5] Pharmacological treatments, such as α1-blockers and 5α-reductase inhibitors (5-ARIs), are associated with long-term adverse effects, including sexual dysfunction and potential neuropsychiatric issues.[6] These drawbacks underscore a persistent clinical need for safer, more tolerable, and effective therapeutic alternatives, which has spurred growing interest in phytotherapy. The pathogenesis of BPH is multifactorial, but chronic inflammation and oxidative stress are now recognized as critical drivers of disease progression.[7] A pro-inflammatory microenvironment within the prostate, characterized by elevated cytokines such as Interleukin-6 (IL-6), is strongly correlated with increased prostate volume and LUTS severity.[8]This inflammation is perpetuated by and linked to persistent oxidative stress, marked by high levels of tissue damage byproducts like Malondialdehyde (MDA).[8] This "oxidative-inflammatory" axis promotes tissue remodeling and cellular proliferation, leading to local inflammatory infiltration, often measured as Tumor-Infiltrating Lymphocytes (TILs) in the stroma. Therefore, agents that can simultaneously target oxidative stress and inflammation represent a highly promising strategy for BPH management. *Cosmos caudatus* Kunth (Kenikir), a plant traditionally consumed in Southeast Asia, has emerged as a potent phytotherapeutic candidate. It is known to be rich in bioactive compounds, including quercetin, kaempferol, and chlorogenic acid, which possess strong antioxidant and anti-inflammatory properties. [9] The potential of its key individual

compounds is established; quercetin, for example, has been shown to suppress oxidative stress in BPH rat models. [10] Furthermore, preliminary studies on the *C. caudatus* extract have confirmed its general safety [11] and *in silico* models have predicted its ability to target IL-6.[12]

However, a significant research gap exists. Despite the strong mechanistic rationale, no comprehensive *in vivo* study has validated the efficacy of the *C. caudatus* whole extract on a BPH model by specifically measuring its impact on this oxidative-inflammatory axis. Previous research has been fragmented: studies were limited to organ-level measurements (prostate weight) without molecular biomarker analysis,[11] were purely computational, [12] or focused on single compounds rather than the synergistic whole extract. [10]

Therefore, this study aimed to investigate the efficacy of an ethanolic extract of *C. caudatus* leaves in a testosterone-induced BPH rat model. We specifically evaluated its ability to attenuate oxidative stress and inflammation by measuring systemic MDA, serum IL-6, and stromal TILs activity, and to determine the resulting impact on prostatic histopathology and organ weight.

Materials and Methods

Plant Material and Extract Preparation

Fresh *Cosmos caudatus* leaves (6–7 weeks old) were collected in 12 April 2024 from a community farm in Pesawaran, Lampung, Indonesia (GPS: 5°24′00″ S, 105°48′00″ E; altitude 150 m). Botanical identification was performed at the Integrated Laboratory, University of Lampung, and verified at the Biology Museum, Universitas Gadjah Mada, with herbarium number MBIOUGM-B00879. The leaves were washed thoroughly with running tap water to remove impurities, chopped, and dried in a cabinet dryer (Memmert UF55, Germany) at 40°C, then milled and sieved through mesh 40. Extraction was carried out using 70% ethanol of analytical grade (Merck, ≥99.8% purity) based on established methods.[11] Three hundred grams of simplicia were macerated at a 1:5 w/v ratio and extracted using a microwave apparatus (Sharp R-21LCF, Japan) at 50°C for 15 minutes. The extract was filtered and the resulting filtrate underwent liquid-liquid partitioning with petroleum ether (Merck, ≥99% purity) at a 1:1 v/v ratio to remove chlorophyll and non-polar lipids.[13] The ethanolic layer was collected and concentrated using a rotary evaporator (Buchi Rotavapor R-300, Switzerland) at 60°C and dried in an oven (Memmert UN30, Germany). Phytochemical characterization included both qualitative and quantitative assays to determine the active compounds responsible for medicinal properties.[9] Tannins were quantified using the Folin–Ciocalteu method (AOAC, 2016) at 760 nm with tannic acid (Sigma-Aldrich, ≥98%) as standard. Alkaloids were determined using the bromocresol green complexation method at 470 nm with quinine (Sigma-Aldrich, ≥98%). Saponins were measured at 435 nm using anisaldehyde–sulfuric acid reagent, while terpenoids were detected qualitatively using thin-layer chromatography on silica gel F254 plates (Merck). All spectrophotometric analyses were performed in triplicate using a UV–Vis spectrophotometer (Shimadzu UV-1800, Japan). Volatile compounds were analyzed by GC-MS using a Thermo Scientific Trace 1310 system (USA) with an HP-5MS UI capillary column. LC-MS/MS analysis of non-volatile constituents was conducted at Saraswati Indo Genetech Laboratory using a Waters Xevo G2-XS QToF (USA) in both ESI+ and ESI− modes, consistent with recent metabolomic studies on *C. caudatus*.[13] Quercetin quantification was performed using a Knauer Smartline RP-HPLC system (Germany) with a C18 column and a mobile phase consisting of methanol and 0.5% phosphoric acid (40:60), set at a detection wavelength of 370 nm using a certified quercetin standard (Sigma-Aldrich, ≥95%).

Male *Rattus norvegicus* (Wistar strain; 6–8 weeks old; 200–250 g) were obtained from the Laboratory Animal Unit, Universitas Sebelas Maret, Surakarta, Indonesia. Rats were housed under controlled conditions of 23 ± 2°C, 40–70% humidity, and a 12-hour light/dark cycle with ad libitum food and water. All procedures adhered to ARRIVE Guidelines 2.0, the Guideline for Pain and Distress in Laboratory Animals, and the principles of the 3Rs, and were approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sebelas Maret (EC/ID: 06/01/02/HC/2025).

A preliminary induction study was conducted using 15 rats divided into three groups (n=5 per dose) to evaluate testosterone propionate (TP; Sigma-Aldrich, ≥98%) at 3, 5, and 7 mg/kg/day administered subcutaneously for 28 days. The 3 mg/kg/day dose successfully induced BPH, as confirmed by prostate weight, prostate index, and histopathology. A subsequent dose-finding study was performed using 15 BPH-induced rats divided into three groups (n=5 per dose) to examine C. caudatus extract administered orally at 125, 250, and 500 mg/kg/day for 28 days. The 250 mg/kg dose produced the most favorable improvements in oxidative and inflammatory biomarkers and histological structure, and therefore was selected, along with 125 mg/kg, for inclusion in the definitive experiment.

In the definitive study, 30 rats were randomized into five groups: Normal (N), BPH control (KN), Finasteride control (KP; 0.44 mg/kg/day orally; Interbat, Indonesia), and two groups receiving *C. caudatus* extract at 125 mg/kg (P1) and 250 mg/kg (P2). All treatments were administered for 28 days following the induction phase. Vehicle control consisted of 0.5% CMC-Na (Brataco, Indonesia).

Blood samples (0.5–1 mL) were collected from the retro-orbital plexus at baseline (T0), post-induction (T1), and post-treatment (T2). Serum MDA and IL-6 were quantified using ELISA kits (FineTest Biotech, Wuhan, China) according to the manufacturer's protocol, and absorbance was read at 450 nm using the Stat Fax 2100 Microplate Reader (Awareness Technology Inc., USA). All assays were performed in triplicate. At the end of the study, animals were euthanized under ketamine–xylazine anesthesia followed by cervical dislocation. The prostate was excised, weighed using an analytical balance (Ohaus Pioneer, USA; precision 0.001 g), and fixed in 10% neutral-buffered formalin. Tissues were processed into FFPE blocks, sectioned at 3–4 µm, and stained with hematoxylin and eosin. Epithelial thickness was measured in five high-power fields (HPF; 400× magnification) using ImageJ software (version 1.53, NIH), and stromal TILs were counted in five fields and averaged.

Prostate index was calculated as prostate weight divided by body weight multiplied by 1,000. Statistical analysis was performed using SPSS version 24.0 (IBM Corp., USA). Data normality was assessed using the Shapiro–Wilk test and homogeneity using Levene's test. Repeated-measures ANOVA with Bonferroni post-hoc correction was applied for MDA and IL-6, one-way ANOVA with Tukey's test for epithelial thickness, and the Kruskal–Wallis test followed by Mann–Whitney U test for prostate weight, prostate index, and TILs. Statistical significance was defined as $p < 0.05$.

Results and Discussion

Extract Characterization

The phytochemical screening of the *C. caudatus* extract confirmed the presence of several key bioactive compounds. The most abundant components were total phenolics and tannins, as detailed in Table 1. GC-MS analysis identified volatile compounds (Figure 1), while LC-MS/MS successfully identified key non-volatile bioactive compounds known for their anti-inflammatory and antioxidant properties, including Kaempferol and Chlorogenic Acid (Table 2, Figures 2-3). To confirm and quantify the primary active flavonoid, Quercetin, HPLC analysis was performed. The chromatogram (Figure 4) shows a peak corresponding to the Quercetin standard, confirming its presence. To confirm and quantify the primary active flavonoid, Quercetin, HPLC analysis was performed. The chromatogram (Figure 5) shows a peak corresponding to the Quercetin standard, confirming its presence.

Preliminary Dose-Finding Study

A preliminary study was conducted to determine the optimal therapeutic dose of the extract. BPH-induced rats were treated with 125 mg/kg (Dose I), 250 mg/kg (Dose II), and 500 mg/kg (Dose III). Histological analysis (Figure 6) showed a dose-dependent improvement, with the 250 mg/kg dose (Dose II) showing significant restoration of acinar morphology and reduced epithelial thickness. Based on these findings and the biomarker data (MDA, IL-6), the 125 mg/kg and 250 mg/kg doses were selected for the definitive study.

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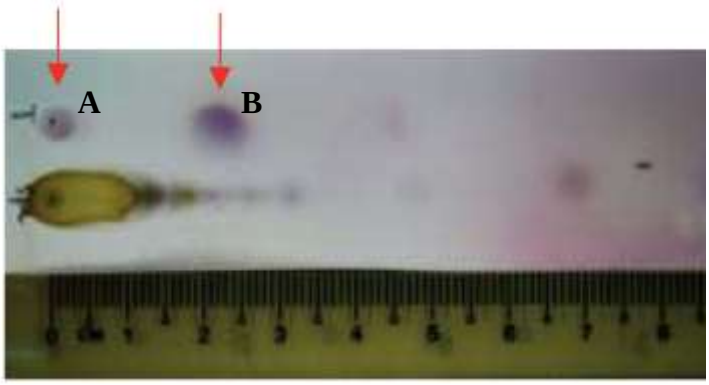

Figure 1: Chromatogram of the crude ethanolic extract of *C. caudatus* detected the presence of terpenoid compounds. (A) Terpineol and (B) Ethanolic leaf extract of *C. caudatus*. GC-MS analysis was performed to identify the volatile compounds within the extract.

Table 1: Phytochemical content of the *C. caudatus* crude extract

No	Compound	Concentration (mg/g)
1	Tannins	**91.17**
2	Total phenolics	**114.33**
3	Total flavonoids	**7.66**
4	Saponin	**12.64**
5	Total Alkaloid	**0.68**

Table 2: Bioactive compounds identified by LC-MS/MS analysis

ESI Mode	Compound Name	Component Group
+	Kaempferol 3-*O*-*β*-glucuronopyranoside	**Flavonoid**
+	Quercetin-3-*O*-arabinoside	**Flavonoid**
+/-	Chlorogenic Acid	**Organic Acid**

Definitive Study: Effect on Oxidative Stress and Inflammation

The definitive study assessed the effect of *C. caudatus* on key biomarkers in five groups (N, KN, KP, P1-125mg, P2-250mg). Testosterone administration significantly increased MDA levels at Time 1 (T1) and T2 in the BPH control (KN) group, indicating high oxidative stress ($p < 0.05$). Treatment with both *C. caudatus* doses (P1, P2) and Finasteride (KP) significantly reduced MDA levels at T2 (Post-Intervention) compared to the KN group ($p < 0.05$) (Figure 7).

Similarly, IL-6 levels were significantly elevated in the KN group at T1 and T2, confirming inflammation. Both extract doses (P1, P2) and Finasteride (KP) effectively suppressed this increase, significantly lowering IL-6 concentrations at T2 compared to the untreated KN group ($p < 0.05$) (Figure 8). To confirm the anti-inflammatory effect at the tissue level, stromal TILs were quantified. The KN group showed the highest mean rank of TILs activity, indicating severe inflammation. All treatment groups (KP, P1, P2) showed significantly lower TILs activity compared to the KN group ($p < 0.05$) (Figure 9).

Definitive Study: Organometric

The impact of the treatment on the physical structure of the prostate was assessed. The KN group showed a significant increase in prostate weight ($p = 0.025$) and prostate index ($p = 0.023$) compared to the normal (N) group. Treatment with Finasteride (KP), 125 mg/kg (P1), and 250 mg/kg (P2) all resulted in a significant reduction in both mean rank prostate weight (Figure 10) and mean rank prostate index (Figure 11) compared to the untreated KN group. Specifically, for prostate weight, significant reductions were observed in KP ($p = 0.025$) and P2 ($p = 0.025$). For prostate index, significant reductions were observed in KP ($p = 0.024$), P1 ($p = 0.050$), and P2 ($p = 0.006$).

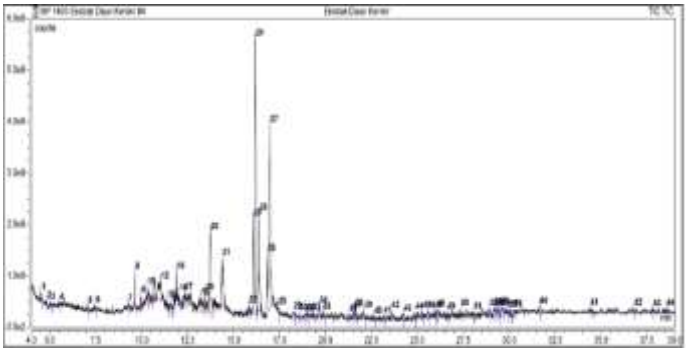

Figure 2: GC-MS chromatogram of the *C. caudatus* ethanolic extract

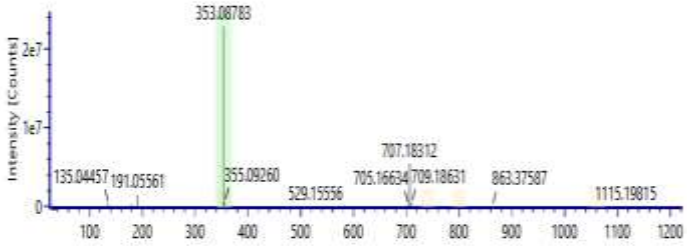

Figure 3: LC-MS/MS mass spectrum of Chlorogenic Acid identified in the *Cosmos caudatus* ethanolic extract. The deprotonated molecular ion peak [M−H]− was detected at m/z 353.09 in negative ionization mode (ESI-).

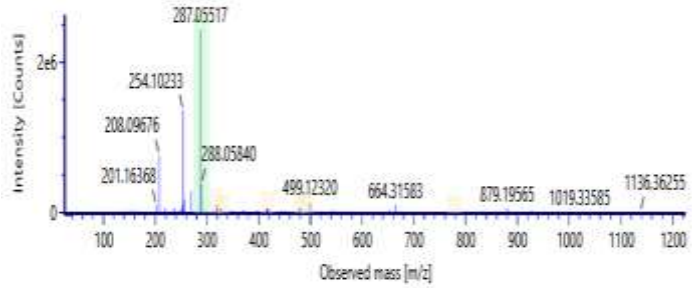

Figure 4: LC-MS/MS mass spectrum of Kaempferol identified in the *Cosmos caudatus* ethanolic extract. The protonated molecular ion peak [M+H]+ was detected at m/z 287.06 in positive ionization mode (ESI+)

The preliminary study confirmed that the BPH induction model using 3 mg/kg/day of testosterone propionate (TP) was successful, marked by significant prostatic hyperplasia. Characterization of the *C. caudatus* ethanolic extract confirmed the presence of key bioactive contents, including phenolics, tannins, and flavonoids, as well as the specific identification of Quercetin, Kaempferol, and Chlorogenic Acid.

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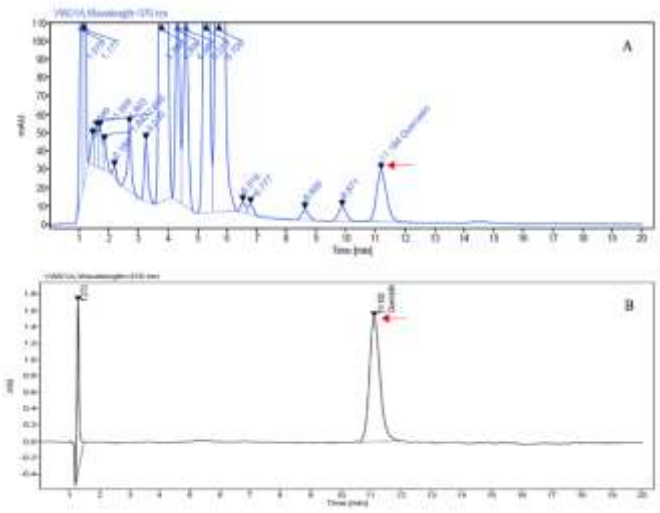

Figure 5: HPLC chromatogram analysis for Quercetin. (A) *C. caudatus* extract. (B) Quercetin standard.

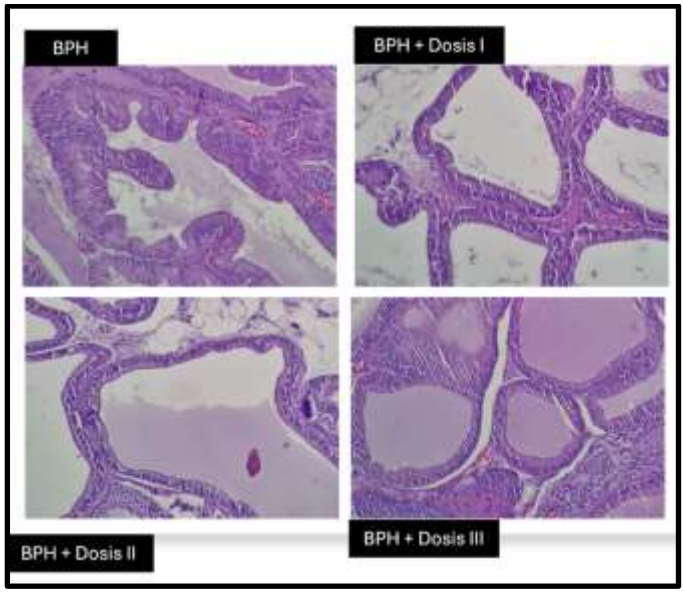

Figure 6: Representative histological sections of prostate tissue in the dose-finding study (A) BPH control; (B) BPH + 125 mg/kg (Dose I); (C) BPH + 250 mg/kg (Dose II); (D) BPH + 500 mg/kg (Dose III)

The identification of these compounds, particularly flavonoids like quercetin and kaempferol, provides a strong mechanistic rationale for the extract's therapeutic potential in targeting the oxidative-inflammatory axis in BPH.[14,15]

In the definitive study, the BPH control group (KN) showed a significant increase in all pathological parameters compared to the normal group (N) ($p < 0.05$). This was observed in elevated oxidative stress (MDA), systemic inflammation (IL-6), local inflammatory infiltration (TILs), and a marked increase in prostate weight and prostate index. These findings confirm that the TP-induced BPH model successfully replicated a state of hyperplasia mediated by a strong oxidative-inflammatory axis, consistent with literature showing a link between androgen induction, inflammation, and tissue proliferation.[16–18]

The primary mechanism evaluated in this study was the ability of *C. caudatus* extract to suppress the "oxidative-inflammatory" axis. Malondialdehyde (MDA), a key marker of lipid peroxidation and oxidative stress, was significantly reduced by both extract doses (P1-125mg and P2-250mg) as well as by Finasteride (KP) ($p < 0.05$). This decrease in MDA levels reflects reduced lipid peroxidation, likely due to the antioxidant activity of the extract's flavonoids which are known to modulate ROS and support endogenous antioxidant systems.[19]

Concurrently, the extract demonstrated a strong anti-inflammatory effect. Serum Interleukin-6 (IL-6), a pro-inflammatory cytokine strongly implicated in BPH progression was significantly suppressed by both treatment doses (P1 and P2) and by Finasteride (KP**)** **(**$p < 0.05$). This supports the hypothesis that phytoconstituents in the *C. caudatus* extract, such as quercetin and kaempferol, can suppress inflammatory pathways by inhibiting NF-κB/STAT-3 transcription and activating the Nrf2/HO-1 pathway.[14,19,20]

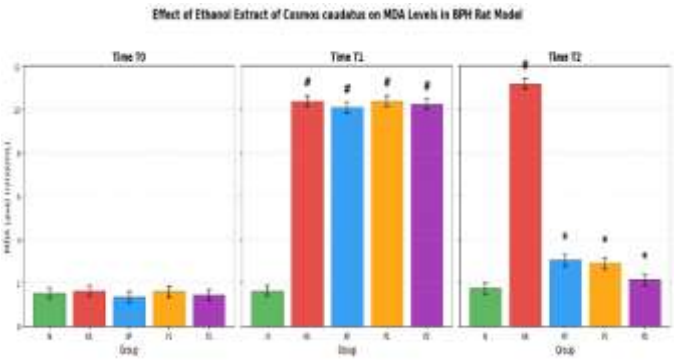

Figure 7: Effect of *C. caudatus* on serum MDA levels (nmol/mL) at T0 (Baseline), T1 (Post-Induction), and T2 (Post-Intervention).

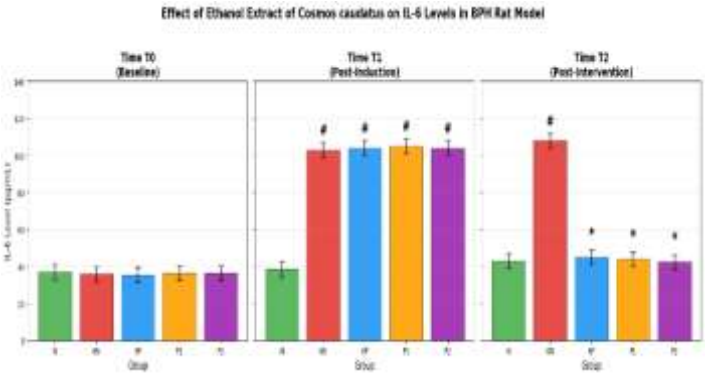

Figure 8: Effect of *C. caudatus* on serum IL-6 concentrations (pg/mL) at T0, T1, and T2.

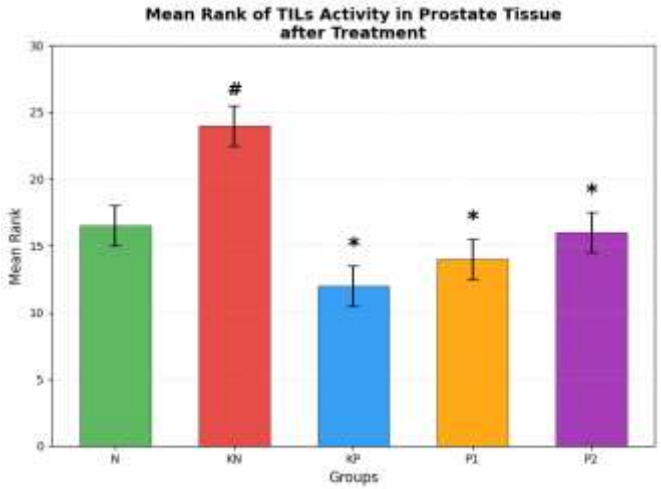

Figure 9: Mean Rank of TILs Activity in Prostate Tissue after Treatment.

This systemic anti-inflammatory effect was confirmed at the tissue level. The BPH control group (KN) showed the highest mean rank of stromal Tumor-Infiltrating Lymphocytes (TILs), indicating severe chronic local inflammation.[17,21] All treatment groups (KP, P1, and P2) successfully and significantly reduced this lymphocytic infiltration. This finding indicates the agents were successful in suppressing inflammatory activity and modulating the local immune response within the prostate tissue, a mechanism linked to the immunomodulatory properties of flavonoids.[13,22] The mitigation of oxidative stress and inflammation translated directly to improvements in the primary pathological outcomes: organ enlargement. The KN group showed a significant increase in prostate weight and prostate index, the hallmarks of BPH.[23] Treatment with *C. caudatus* extract at both doses (P1-125mg and P2-250mg), as well as the positive control Finasteride (KP), resulted in a significant reduction in the mean rank of prostate weight and prostate index **(**$p < 0.05$). This demonstrates that the molecular and cellular benefits of the extract (reducing MDA, IL-6, and TILs) were effective in inhibiting or reversing the physical tissue hyperplasia.[5,24]

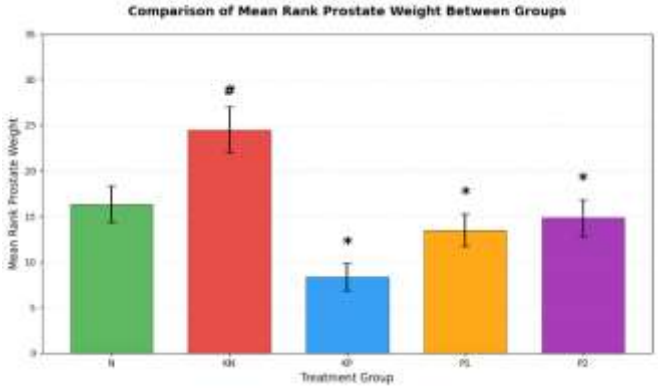

Figure 10: Comparison of Mean Rank Prostate Weight Between Groups.

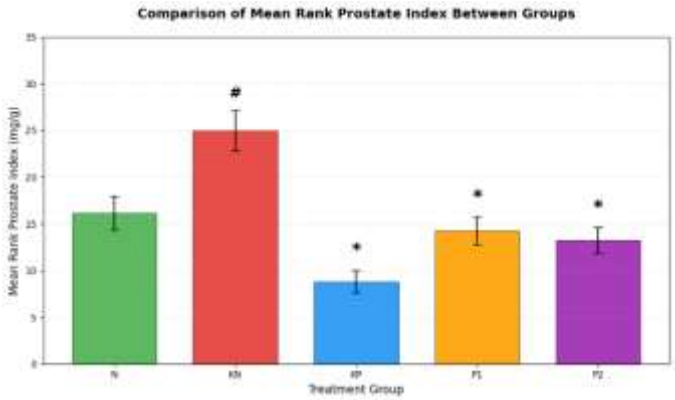

Figure 11: Comparison of Mean Rank Prostate Index Between Groups

The antiproliferative effect of the extract likely operates via a non-hormonal, non-enzymatic mechanism, linked to the antioxidant (Nrf2/HO-1 activation) and transcriptional modulation (PI3K/Akt and NF-κB inhibition) activities of its flavonoid compounds.[25,26] Notably, the efficacy of the extract, at both the 125mg (P1) and 250mg (P2) doses, was comparable to the standard pharmaceutical Finasteride (KP) across all measured parameters. This suggests that a phytotherapeutic approach targeting redox balance and inflammation can achieve an antiproliferative effect equivalent to that of standard hormonal pathway inhibitors.[27,28]

Overall, this study demonstrates that *C. caudatus* ethanolic extract acts as an effective multi-target agent. It works through a dual anti-oxidant and anti-inflammatory mechanism to achieve an efficacy comparable to Finasteride in this BPH model, positioning it as a potent phytotherapeutic candidate.

Conclusion

The administration of *Cosmos caudatus* ethanol extract, at both 125 mg/kg (P1) and 250 mg/kg (P2), significantly inhibited the progression of testosterone-induced benign prostatic hyperplasia (BPH) in a rat model ($p < 0.05$). This therapeutic effect was demonstrated to be mediated by a potent anti-oxidant and anti-inflammatory mechanism. The extract significantly reduced the systemic oxidative stress marker (MDA) and the pro-inflammatory cytokine (IL-6). This anti-inflammatory action was further confirmed at the tissue level by a significant reduction in stromal lymphocytic infiltration (TILs) ($p < 0.05$).

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

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