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Research Article

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Cross-talk of Androgen & Cytokine Signalling in Breast Cancer

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HIGHLIGHTS

- IL-6 activates androgen receptor signaling
- DHT suppresses inflammatory cytokine responses
- STAT3 mediates AR pathway activation
- Bicalutamide inhibits mammary tumor growth
- AR signaling regulates immune responses

Key Words:
Breast cancer
Androgen receptor
Dihydrotestosterone
IL-6
Cytokines
JAK/STAT signaling
Inflammation
Tumor microenvironment
4T1 model
Immunomodulation

ABSTRACT

Introduction: Breast cancer progression is strongly influenced by the tumor microenvironment, where inflammatory cytokines and androgen receptor (AR) signaling regulate tumor growth, immune responses, and disease progression. Understanding the interaction between cytokines and AR signaling may provide novel therapeutic strategies. **Aim & Objective:** To investigate the effects of inflammatory cytokines and dihydrotestosterone (DHT) on breast cancer cell proliferation, AR signaling, inflammatory pathways, immune modulation, and tumor progression using in vitro and in vivo models. **Materials & Methods:** MCF-7 breast cancer cells were treated with IL-6, IL-10, TNF-α, and DHT to evaluate cell proliferation, AR signaling, and inflammatory gene expression. The involvement of the JAK/STAT pathway was examined using the inhibitor AG490. In vivo, mouse mammary tumor and 4T1 tumor models were used to assess inflammatory responses, tumor growth, and immune cell populations following DHT and bicalutamide treatment. **Results:** IL-6 significantly enhanced MCF-7 cell proliferation and upregulated AR, prostate-specific antigen (PSA), and p21 expression in a dose- and time-dependent manner, whereas IL-10 inhibited these effects. AG490 abolished IL-6-induced AR activation, confirming STAT3-dependent signaling. DHT suppressed TNF-α production, modulated inflammatory mediators, and differentially regulated cytokine expression. In vivo, DHT attenuated lipopolysaccharide-induced inflammation through AR signaling, while bicalutamide reversed these effects. Bicalutamide significantly reduced 4T1 tumor growth, whereas DHT produced modest tumor regression and increased splenic $CD8^+$, $CD4^+$, and regulatory T-cell populations. **Conclusion:** Cytokine-mediated AR signaling plays a pivotal role in breast cancer progression and immune regulation. Targeting AR-associated inflammatory pathways may offer a promising therapeutic approach for breast cancer.

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INTRODUCTION

Breast cancer is the most commonly diagnosed malignancy among women worldwide and is the second leading cause of cancer-related deaths. It is more prevalent in developed countries; however, its incidence is increasing rapidly in developing nations. In India, breast cancer is the second most common cancer among women after cervical cancer. Breast cancer is a heterogeneous disease characterized by diverse molecular profiles. Steroid hormone receptors play an important role in its pathogenesis and progression.

Based on estrogen receptor (ER) status, breast cancer is broadly classified into ER-positive (ER+) and ER-negative (ER−) tumors. Approximately 70–80% of breast cancers are ER-positive, whereas 20–30% are ER-negative. Triple-negative breast cancer (TNBC), characterized by the absence of ER, progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2/neu), accounts for approximately 10–15% of all breast cancers and represents the most aggressive subtype. Progesterone receptor expression is observed in nearly 50–70% of breast cancers.

Another important steroid hormone receptor is the androgen receptor (AR). Several studies have demonstrated that AR is expressed in approximately 70–90% of breast carcinomas [1–9]. AR also plays an essential role in normal breast development. During puberty, AR is expressed in nearly 20% of breast epithelial cells, whereas ER is expressed in only about 10% of cells. Although the precise role of AR in breast carcinogenesis remains incompletely understood, AR positivity has been associated with distinct clinicopathological characteristics in different molecular subtypes of breast cancer.

AR is one of the most frequently expressed steroid hormone receptors in in-situ, invasive, and metastatic breast carcinomas [9]. Approximately 60–70% of breast cancers express AR irrespective of ER and PR status [2,10,11]. AR is frequently co-expressed with other steroid hormone receptors, and HER2 overexpression has been reported to correlate significantly with AR positivity [12–16]. Furthermore, approximately 90–95% of ER-positive tumors and 10–43% of TNBCs express AR [14,10,11,15]. AR expression has also been identified in nearly 25% of metastatic breast cancers [16–18].

Immunohistochemical studies have demonstrated that AR expression varies considerably among different molecular subtypes of breast cancer, with the highest positivity observed in Luminal A tumors and comparatively lower expression in TNBC [19,20,4]. AR has also emerged as a potential predictor of response to endocrine therapy. Castellano et al. reported that AR positivity was associated with an approximately 30% reduction in mortality among patients with ER-positive breast cancer [21].

In ER-positive breast cancers, AR expression has been associated with lower tumor grade, reduced lymph node metastasis, prolonged disease-free survival, and improved prognosis [22–25,10]. Experimental evidence suggests that AR exerts an anti-proliferative effect by antagonizing ER signaling and inhibiting estradiol-mediated ER transcriptional activity [26]. Conversely, in ER-negative breast cancers, AR signaling may promote tumor growth through an AR-dependent pathway [27]. Nevertheless, AR-positive ER-negative tumors generally demonstrate better disease-free survival and a more favorable prognosis than AR-negative tumors [10,22].

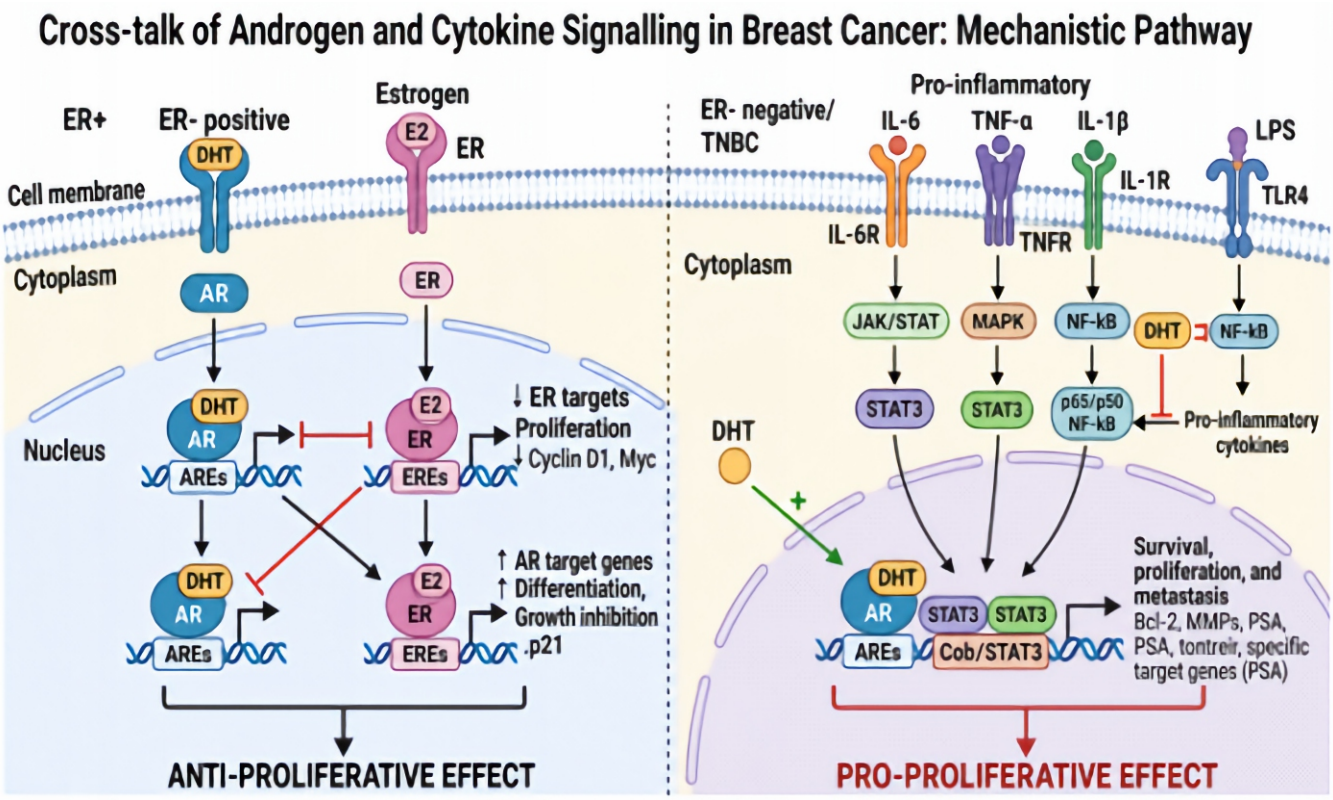


Figure 1: Mechanistic cross-talk between androgen receptor and cytokine signaling pathways in breast cancer.

Tsang et al. reported that the favorable prognostic significance of AR positivity was evident primarily in HER2-positive disease, whereas no significant improvement in overall or disease-free survival was observed in HER2-negative Luminal B breast cancers [28]. The prognostic significance of AR in TNBC remains controversial. While some studies found no association between AR expression and patient outcomes [29], others reported improved prognosis and survival among AR-positive TNBC patients [30–32]. Overall, current evidence suggests that AR expression is generally associated with favorable clinical outcomes in breast cancer.

Targeting the androgen receptor has long been an effective therapeutic strategy in prostate cancer. Historically, exogenous androgen therapy was also used in the management of ER-positive breast cancer before the 1970s. Androgens continue to be used in selected conditions such as amenorrhea, androgenic alopecia, hirsutism, and ovarian cancer [33,34]. More recently, AR has emerged as a promising therapeutic target in ER-positive disease and molecular apocrine breast cancer. Anti-androgen agents such as enzalutamide (ClinicalTrials.gov Identifier: NCT01889238) and CYP17 inhibitors including abiraterone acetate (NCT00755885) and orteronel (NCT01990209) are currently under clinical evaluation for AR-positive breast cancer [9].

Cytokines are the low molecular, inducible proteins that required in pico-molar concentration for their biological activity. Both androgen and cytokines play important role in the initiation and progression of breast cancer so in the present study we have evaluated the effect of different cytokines on the expression of AR and its target genes (PSA, p21). We have also evaluated the effect of dihydrotesterone (DHT) an non aromatizable androgen on the expression of the different cytokines and its profile in both in vitro and invivo mice model. We have also checked the effect of DHT on the lipopolysaccharide induced inflammatory response in both in vitro and invivo conditions. **Figure 1.** Mechanistic model illustrating the cross-talk between androgen receptor signaling and inflammatory cytokine pathways in ER-positive and ER-negative/triple-negative breast cancer, highlighting the anti-proliferative role of AR in ER-positive tumors and its pro-proliferative interaction with STAT3/NF-κB signaling in TNBC.

Materials & Methods

Reagents: All the reagents were procured from Sigma Aldrich unless otherwise specified.

Cell culture Maintenance: Breast cancer cells MCF-7 and 4T1 cells were cultured in 10% RPMI medium and maintained at 5% CO_2 under humid conditions.

MTT Assay: $10X10^4$ cells were seeded in 96 well plates and allowed to grow for 24h. Cells were pre-treated with lipo-polysaccharide (1µg) followed by treatment with different concentrations of DHT alone or in the presence of its antagonist, bicalutamide. At the end of treatment 20 µl (5mg/mL) Tetraazolium dye was added in each well and incubated for 2h at the end of incubation media were removed and formazan crystal formed were dissolved in 200µl DMSO. Optical density was recorded using ELISA plate reader.

Western Blotting: $1X10^6$ cells were seeded in T25 culture flask and allowed to grow for 24h. Cells were treated with different cytokines or androgen either alone or in the presence of their inhibitors at the end of incubation cells was harvested. RIFA buffered has been added to lysed the cells in the presence of protease and phosphatase inhibitor cocktail. Protein was quantified by Bradford and 40µg protein were loaded on 12% SDS-PAGE gel and electrophoresed. Protein were transfer to PVDF membrane and probed with specific antibodies (AR, PSA, p21, STAT1, 3, 5, 6, NFkB, JAK1, ICAM-I, VCAM, COX2) for overnight at 4^0C. At the end of incubation blots were washed and probed with corresponding secondary antibodies. Blots were develops by using chemiluminescence, ECL substrate on chemi doc.

Quantitative PCR: Total RNA was isolated using trizol reagent as according to manufacturer instructions and complementary DNA (cDNA) was synthesised using cDNA fermentas kit (K1622).

***In vivo study*:** *In vivo* study was done in mouse mammary tumor model generated after injecting 4T1 cells subcutaneously at mouse mammary fat pad. Tumor generated within a week. Mice were divided into four groups and each group has six mices, one group as a vehicle control, one group treated with Bicalutamide (2mg/kg) one group with dihydro-testosterone (DHT) 100µg/animal and group with DHT and bicalutamide for 21days.

CD marker Staining: PBMC cells were isolated from spleen and bone marrow after flushing with PBS and cell suspension was over lay over ficol layer and centrifuged at 400g for 30 minutes. A white ring formed was collected with 1 mL tip and cell was further washed with PBS. PBMC cells were stain with fluorescent tagged CD3, CD8, CD4, CD11c, CD11b, F4/80, CD25 antibodies for 45 minutes and samples were acquired by flow cytometry using FACScaliber.

Cytometric Bead Array: Level of different serum cytokines were measured by cytometric bead array (BD biosciences, USA) as per manufacturer instructions. Briefly, 50µl samples were incubated with 50 µl mixed capture beads and 50 µl detection reagent for 3h at room temperature in dark. At the end of incubation samples were washed with 1mL washed buffer, centrifuged (200g), and re-suspended in 300 µl wash buffer. Samples were acquired using FACS Calibur and data were analyzed by FCAP array version 1.0.1 software.

Statistics: All statistical analyses were performed using Prism 5 software, and p value less than 0.05 was considered significant.

RESULTS

Cytokines have an important role in initiation and progression of tumours. To check the effect of cytokines in *in vitro* culture of breast cancer cells, MCF-7 cells were treated with different concentrations of cytokines for 24 h. The results showed that IL-10 and TNF-α significantly reduced cell proliferation, while IL-6 significantly promotes cell proliferation **(Figure 1).** Most of the cytokines support the tumor in various ways but the underline mechanism is not completely known. To test the effect of cytokines, MCF-7 cells were treated with different cytokines and effect on androgen receptor signalling was analysed using western blot. Results suggest that IL-6 significantly induces the expression of androgen receptor and its target genes (PSA, p21) while IL-10 significantly suppresses the expression of AR and its target genes. Furthermore TNF-α and TGF-β does not have effect the level of AR **(Figure 2)**.

Further we have also analysed the effect of IL-6 in dose and time dependent manner. Results showed that IL-6 significantly induces the expression of AR and its target gene PSA in both dose and time dependently **(Figure 3).**

L-6 is a pleiotropic cytokines which act through the JAK-STAT pathway in a STAT3-dependent manner. To check whether IL-6 induces the expression of AR and its target gene in a STAT3-dependent manner, we have pre-treated the MCF-7 cells with AG490, a STAT3 inhibitor that inhibits JAK2 and finally STAT3. Results showed that in the presence of AG490, the IL-6-mediated effect on AR and its target was significantly abrogated **(Figure 4)**.

hese results suggest that the IL-6-mediated induction of AR and its target genes is STAT-mediated. We have also checked the effect of DHT on cytokine profile and its signalling pathways. We have treated the MCF-7 cells with different concentrations of DHT, and cytokine profiling was done by using cytometric bead array. The cytokine profiling results showed that DHT significantly suppresses the production of an inflammatory cytokine, TNF-α, suggesting an anti-inflammatory role of DHT **(Figure 5).**

We have also checked the effect of DHT on different cytokine signalling proteins. MCF-7 cells were treated DHT (10 nM) for different time points. Results suggested that the DHT induces the expression of STAT 5, NFkB (p^{65}) COX2 and JAK1 while it suppresses the STAT3, ICAM-1 **(Figure 6).**

Quantitative PCR results suggested that DHT suppresses the expression of IL-6 and IL-10 at lower concentra-tions (0.1, 1nM) while at higher concentrations it induces the expression of IL-6 and IL-10 genes, & DHT suppresses the expression of IFN-ϒ at all concentrations **(Figure 7)**.

Besides androgen receptor, cytokines have also emerged as important prognostic bio-markers in breast cancer. Lipopoly-saccharide (LPS) binding to Toll-like receptor-4 (TLR4) activates downstream signaling pathways, including mitogen-activated protein kinases (MAPKs) [35] and nuclear factor-kappa B (NF-κB) [36], resulting in macrophage-mediated production of inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and nitric oxide (NO) [37]. To check effect of DHT on the LPS induced inflammatory response we have stimulated the DHT (100 µg/day/animal, 5 day) pretreated mouse mammary tumor model with lipopolysaccharide (3 mg/kg) for three consecutive days. Our results showed that LPS stimulates the inflammatory and LPS stimulation promotes growth of mouse mammary tumor in invivo model.

Furthermore cytokine profiling by cytometric bead array result showed that DHT pretreatment significantly inhibits the LPS induced inflammatory response in in vivo mouse mammary tumor model. Further anti-inflammatry effect of DHT was abrogated in the presence of specific androgen receptor, bicalutamide (Bic.) suggest that above anti-inflammatory effect of DHT is AR mediated. To study the effect of DHT in in vivo mouse mammary tumor model we have inject the 4T1cells in Balb/C mouse at mammary fat pad.

Animals were divided into four groups with 6 animals in each group. First group is treated with vehicle and second group with DHT (100 µg/animal/day), third group was treated with androgen receptor antagonist bicalutamide (2 mg/kg/day) and fourth group was treated with both DHT and Bic. In vivo results suggested that Bic significantly regress the tumor in mouse model although DHT also slightly regresses while the effect combination of both DHT and Bic is intermediate of that of DHT and Bic. Furthermore there is no significant difference in the body weights between the groups was observed **(Figure 8).**

We have also evaluated the effect of DHT on the different immunological cells. Spleen and bone marrow cells were flush out with PBS and PBMC were isolated by using Ficoll gradient centrifugation and PBMC were stained with fluorescent tagged CD markers of different immunological markers. Result showed that DHT significantly increase the number of T-cyto T helper cells & Treg cells in PBMC isolated from spleen while this effect was abrogated in the presence of androgen receptor antagonist **(Figure 9).**

Figure 10: Effect of DHT & its Bic on the different cells of the immune system in Spleen**. Figure 11.** Flow cytometric analysis of dendri-tic cells, T cytotoxic cells, T helper cells, macrophages, and T regulatory cells in bone marrow-derived PBMCs following vehicle, DHT, bicalutamide, and DHT + bicalutamide treatment.

Figure 12: Effect of DHT and its Bic on the different cells of the immune system in Bone Marrow. LPS induced inflammatory response and DHT in Vivo model and in vitro culture by cytokines profiling and Real time analysis **(Figure 13)**.

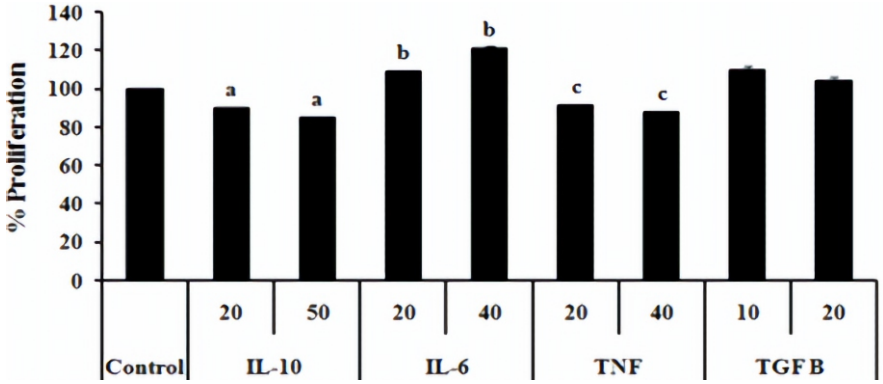


Figure 1: Effect of IL-6, IL-10, and TNF-α on cell proliferation. IL-6 significantly promoted cell proliferation, whereas IL-10 and TNF-α significantly reduced cell proliferation.

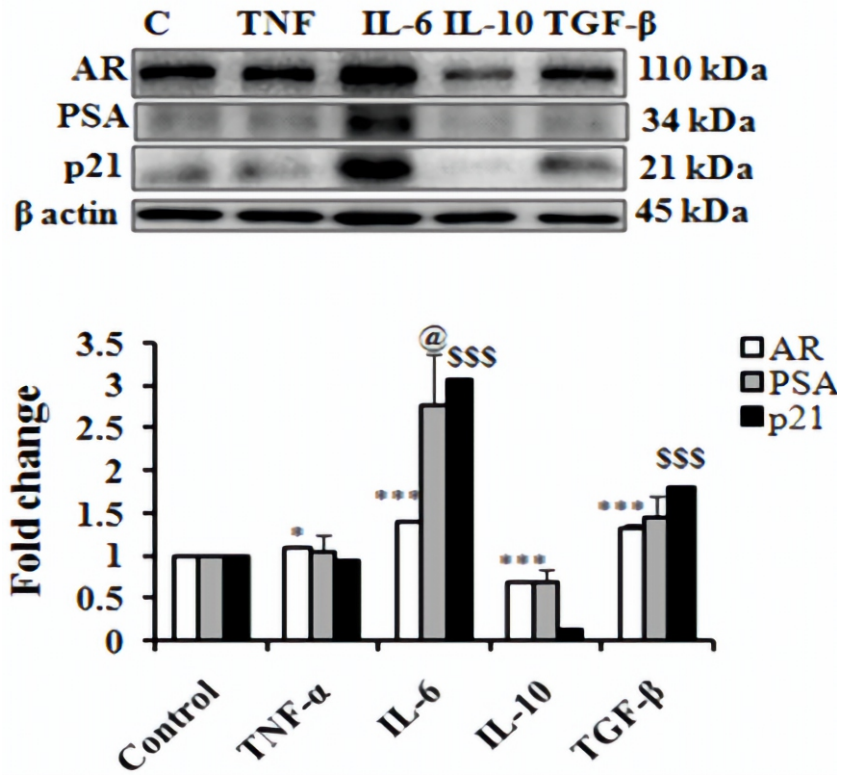


Figure 2: **MCF-7 cells treated with different cytokines TNF-α (20ng/mL), IL-6 (15ng/mL), IL-10 (50ng/mL), TGF-β (1ng/mL).**

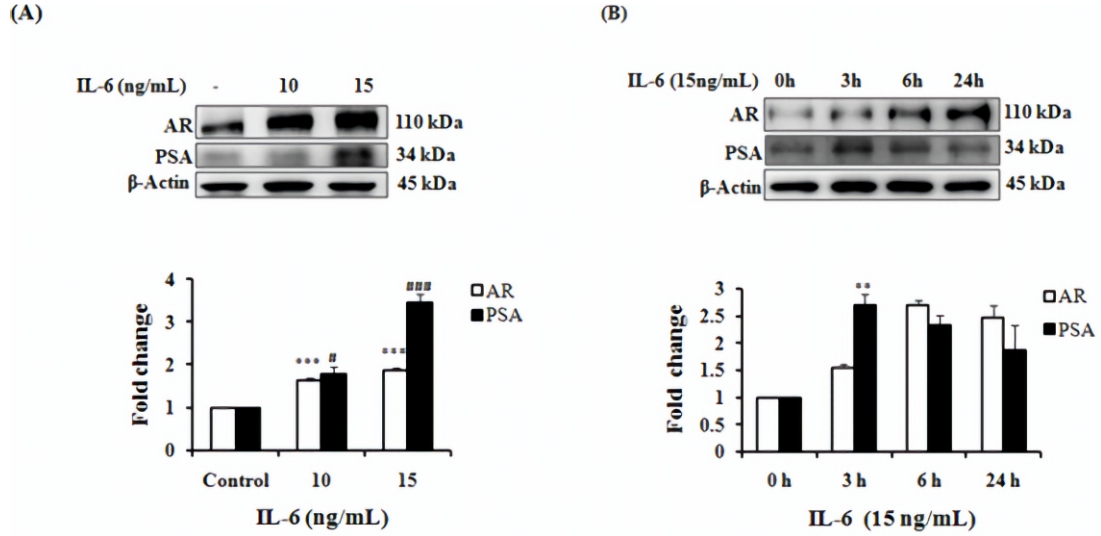


Figure 3: MCF-7 cells were treated with different concentrations at different time points with IL-6.

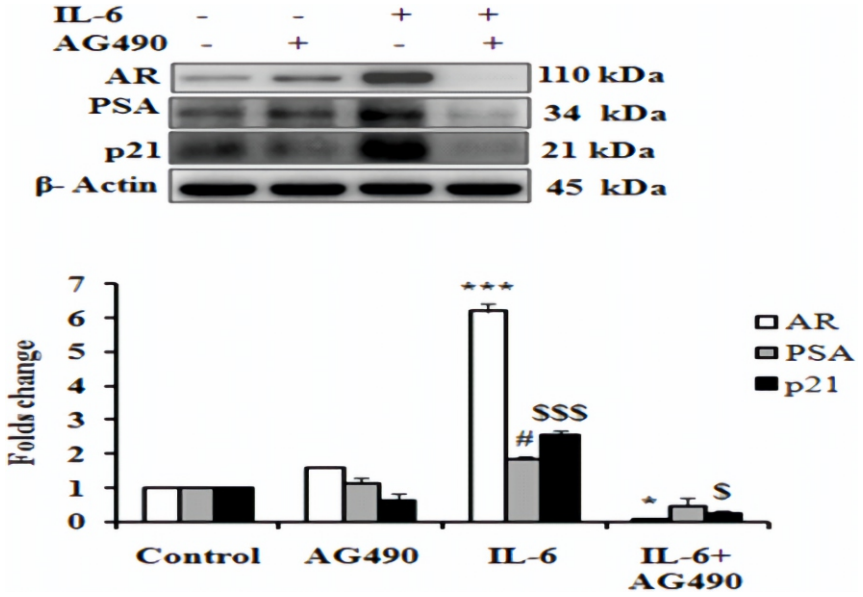


Figure 4: Supporting quantitative PCR Data

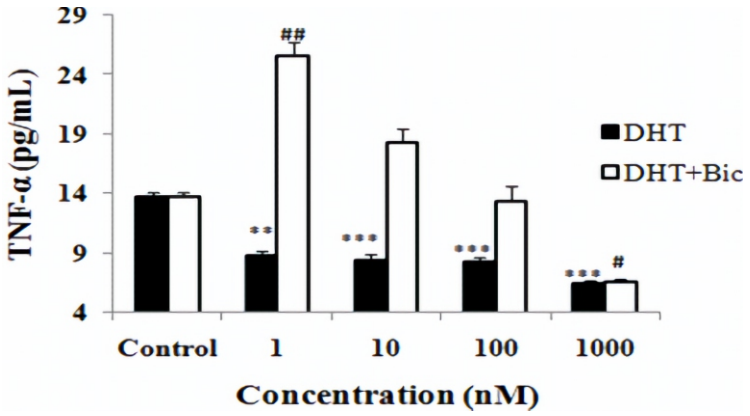


Figure 5: Effect of DHT on cytokine profile in MCF-7 cells.

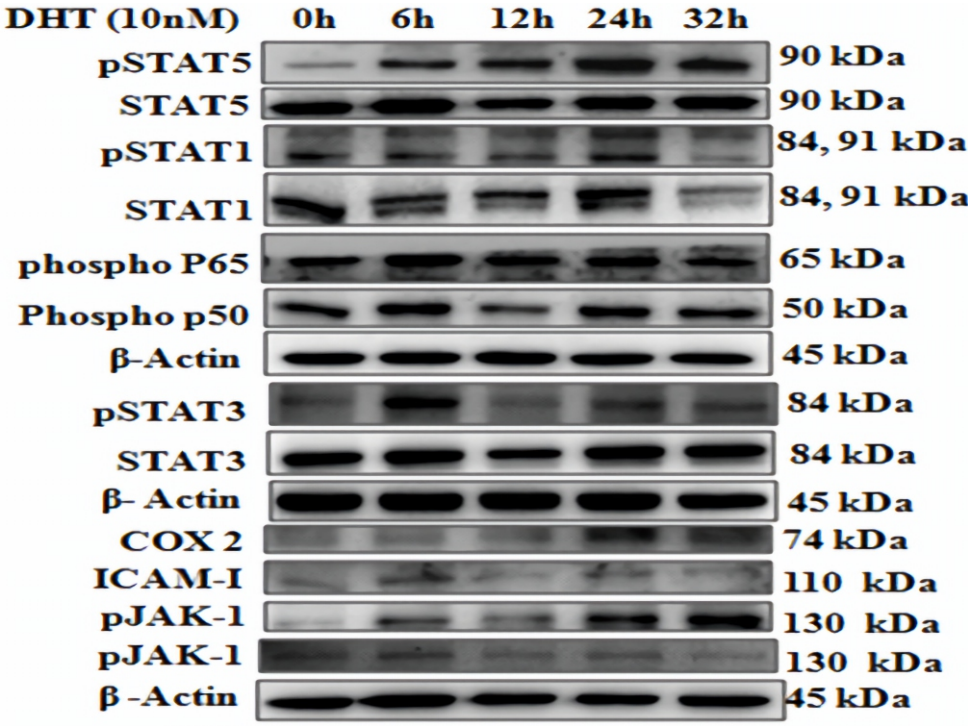


Figure 6: Western blot analysis of cytokine signaling proteins following DHT (10 nM) treatment in MCF-7 cells. DHT increased the expression of STAT5, NF-κB (p65), COX-2, and JAK1, whereas STAT3 and ICAM-1 expression was reduced over the treatment period.

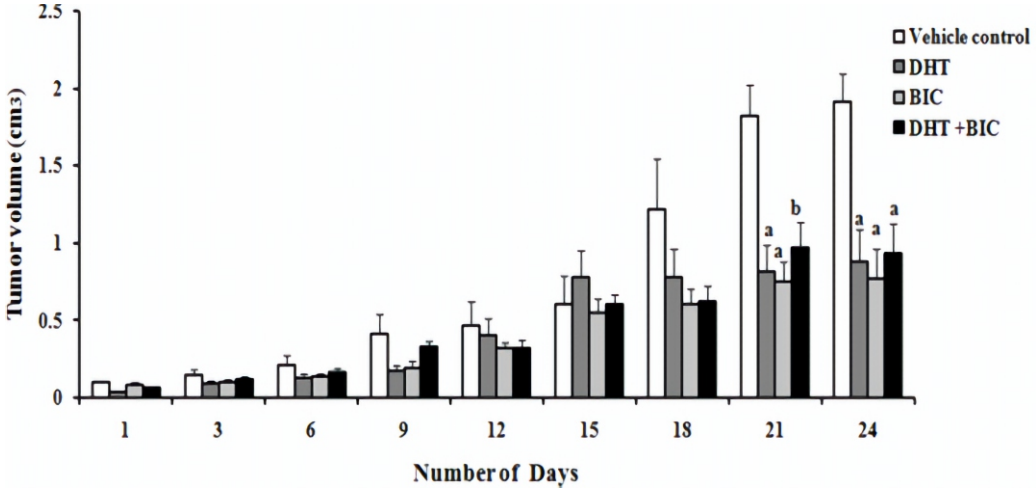


Figure 9: Flow cytometric analysis of spleen-derived PBMCs demonstrating that DHT treatment significantly increased CD8⁺ cytotoxic T cells, CD4⁺ helper T cells, and Treg cells. These immunomodulatory effects were reversed in the presence of the androgen receptor antagonist bicalutamide.

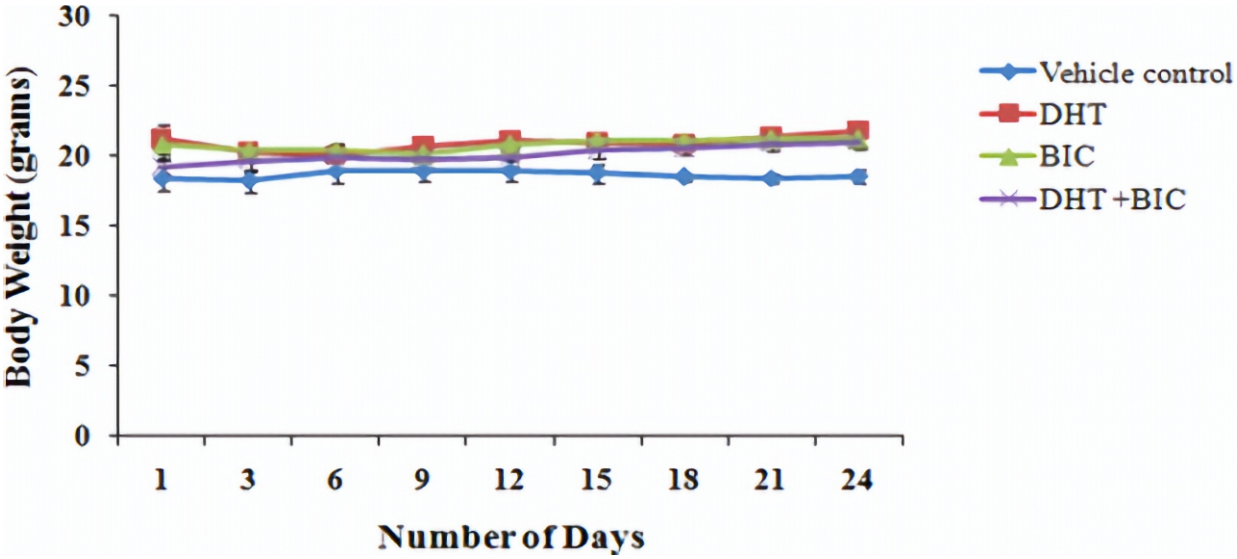
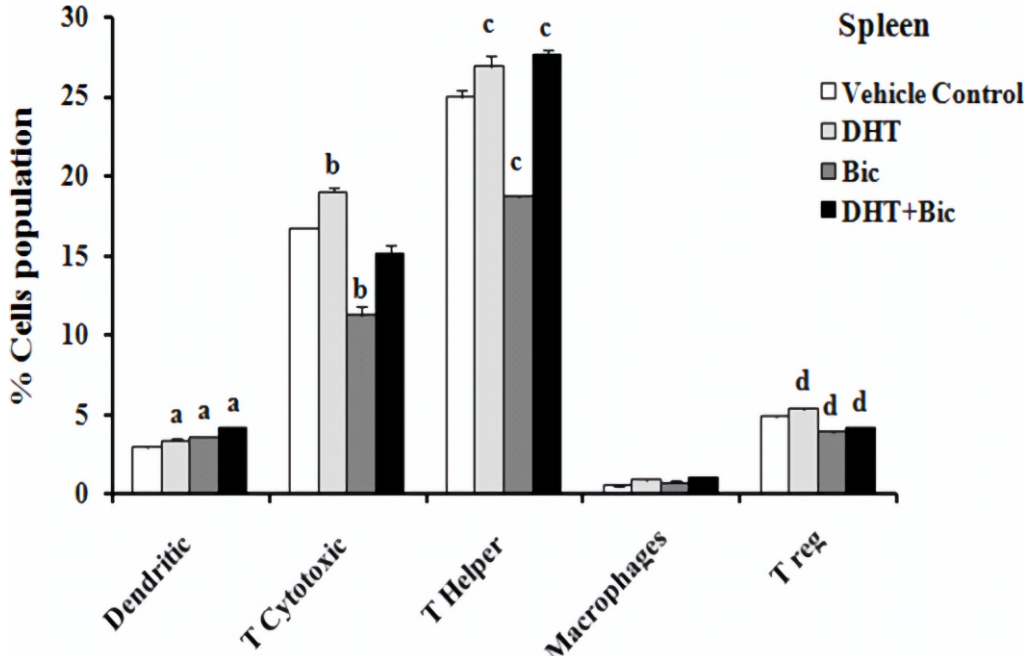


Figure 10: Effect of DHT and its Bic on the different cells of the immune system in Spleen.



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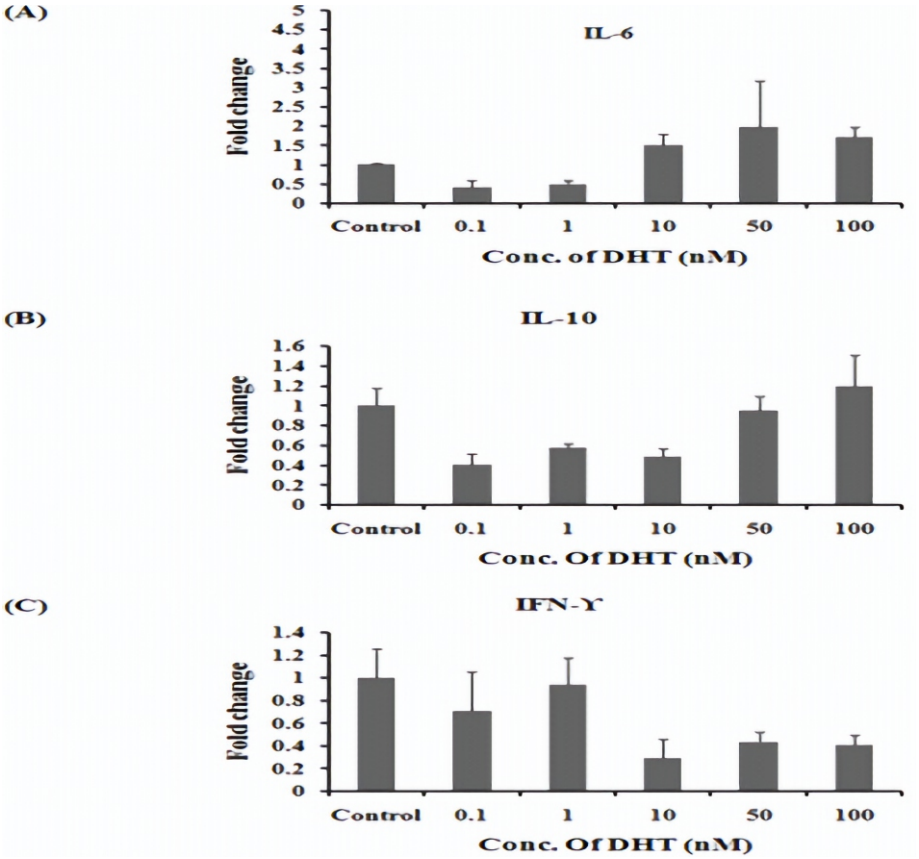

Figure 7: In vivo quantitative PCR analysis demonstrated that dihydrotestosterone (DHT) suppressed the expression of IL-6 and IL-10 at lower concentrations (0.1 and 1 nM), whereas higher concentrations of DHT induced the expression of both cytokines. In contrast, DHT consistently suppressed IFN-γ expression across all tested concentrations.

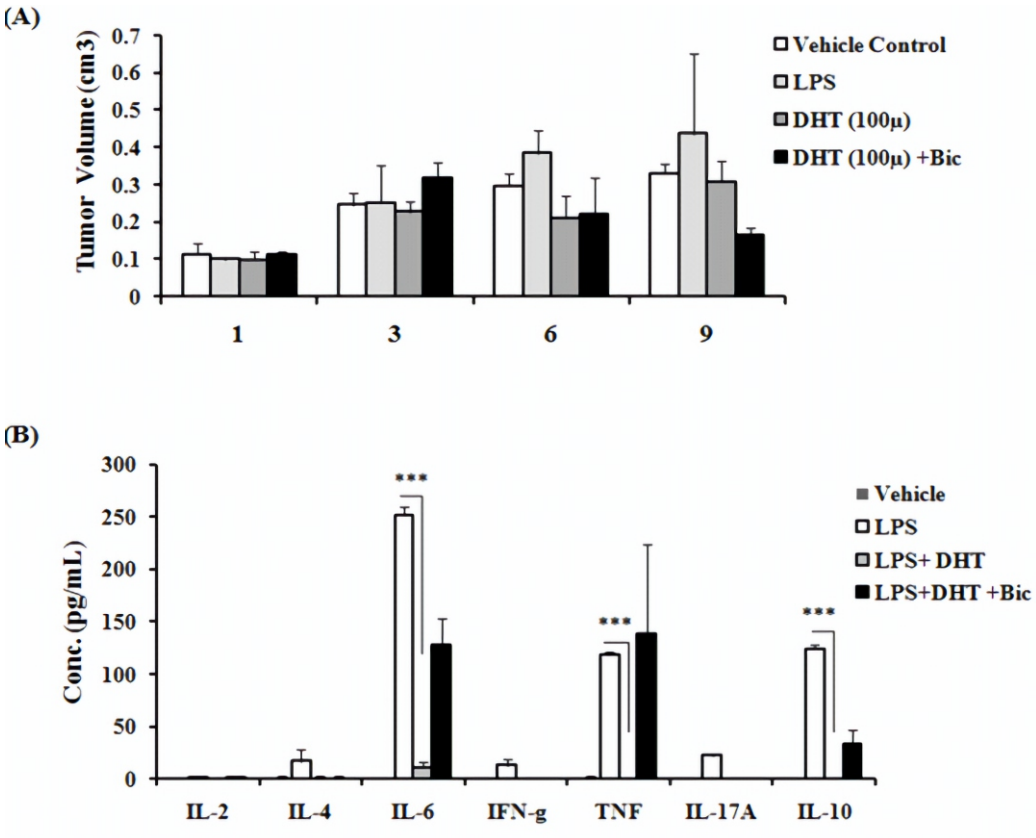

Figure 8. *In vivo* antitumor effects of DHT, bicalutamide, and combination therapy. Bicalutamide produced the greatest tumor regression, while DHT showed a modest inhibitory effect; the combination treatment demonstrated an intermediate response without significant changes in body weight.

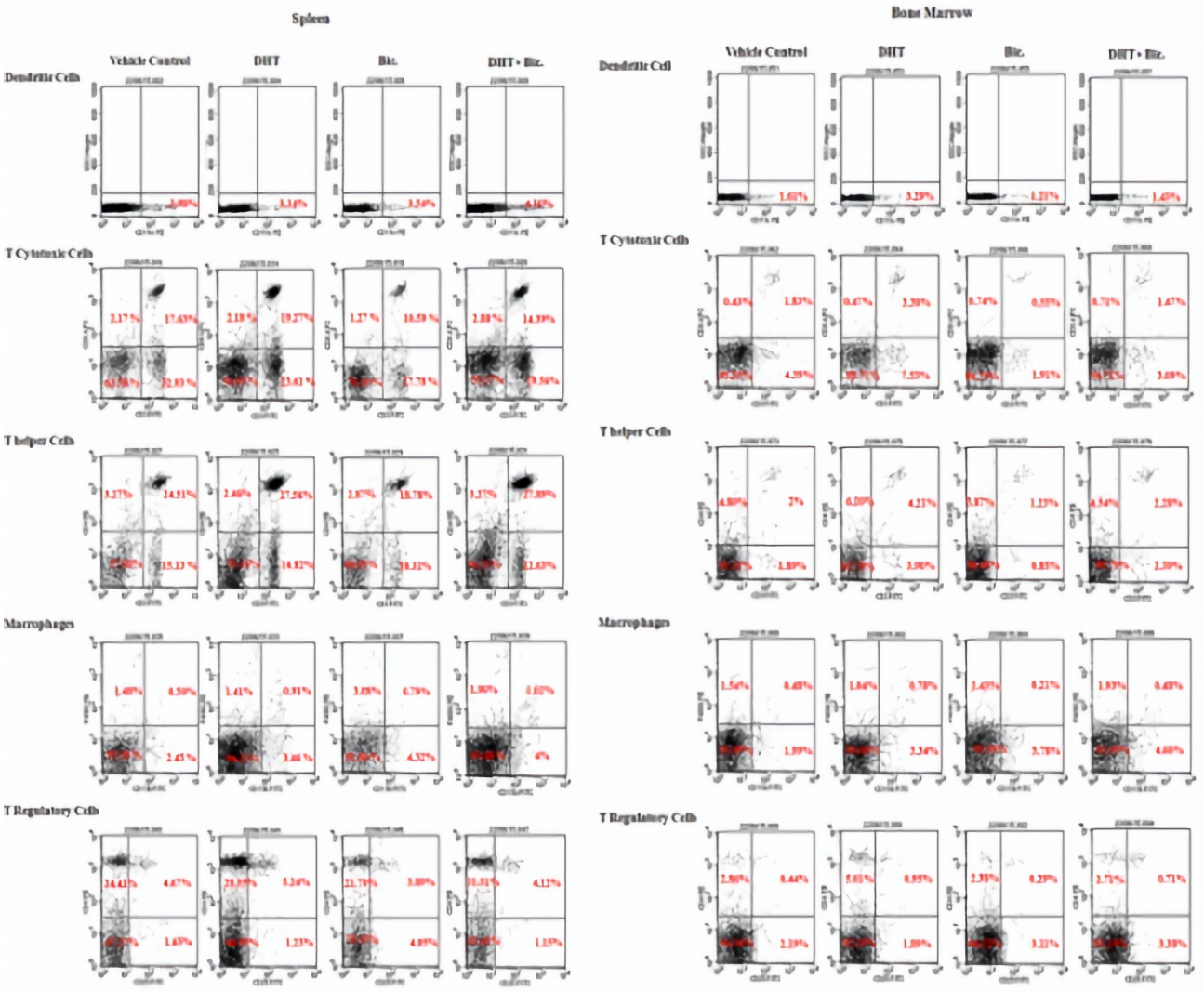

Figure 11. Effect of DHT on serum cytokine profile. DHT significantly reduced the serum levels of **IL-6, TNF-α, and IL-10**, while **IL-2, IL-4, IFN-γ, and IL-17A** remained unchanged.

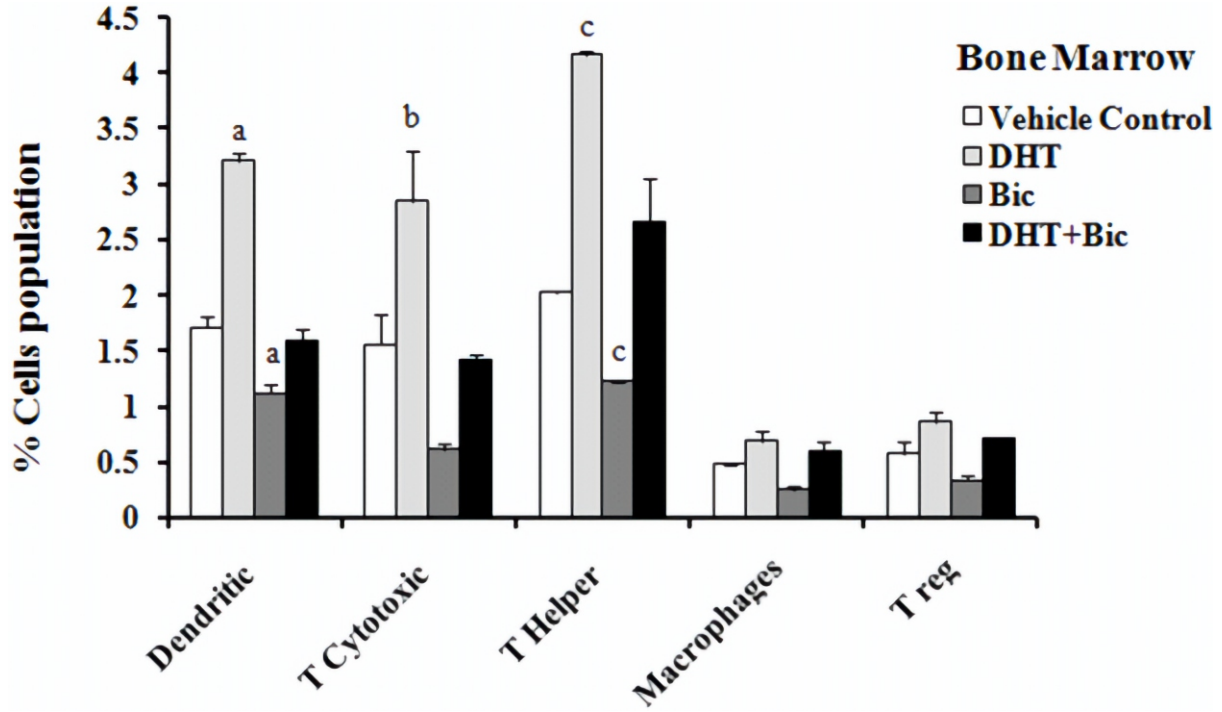

Figure 12: **Effect of DHT and its Bic on the different cells of the immune system in Bone Marrow.**

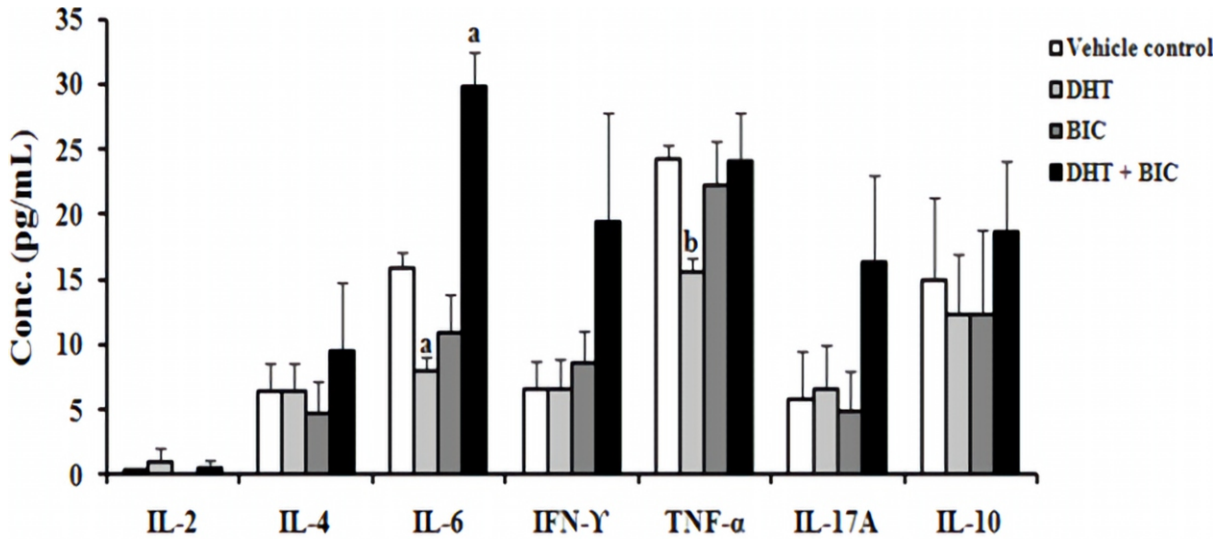

Figure 13: Cytokines Profile in *in vivo* mouse model.

DISCUSSION

Androgen receptor is the most significantly and most abundantly expressed receptor in breast cancer. Several studies reported that androgen receptor is expressed in 70-90% of breast cancer cases irrespective of ER and PR status. Several previous studies suggest the role of androgen and its receptor in the normal development of breast cancer. Androgens are steroid hormones; several previous studies have reported that most of the steroids has immune-suppressive effect. DHT is a non-aromatizable androgen that has maximum affinity for androgen receptor. DHT has been reported to suppress the LPS, TNF-α and IL-1-induced inflammatory response. Our in vitro and in vivo studies suggest that DHT has anti-inflammatory response on LPS induced inflammatory response. Cytokine profiling results in invitro MCF-7 cells supernatant suggest that DHT significantly suppress the TNF-α production by MCF-7 cells. Further our finding also validated by in vivo study in mouse mammary tumor model. Our serum cytokine profiling results suggest that DHT inhibits LPS induced production of IL-6, TNF-α, IL-10.

CONCLUSION

IL-6 and TGF-β promotes while IL-10 and TNF-α inhibits breast cancer (MCF-7) cells proliferation. IL-6 induces the expression of AR and its target gene in dose and time dependent manner in STAT3 dependent manner. *In vitro and in vivo* studies on the effect of DHT on the immune system suggested that the DHT have anti-inflammatory and immunosuppressive role in breast cancer.

LIMITATIONS & FUTURE PERSPECTIVES

The study's limitations include a single-centre setting, a relatively small sample size, and a short study duration, which may limit the broader applicability of the results. Future studies should incorporate multicentre designs with larger populations to enhance validity, assess long-term outcomes, and investigate advanced diagnostic & management approaches. Such efforts will improve overall patient care & help minimize complications.

CLINICAL SIGNIFICANCE

The clinical significance of this study lies in its potential to bridge the gap between research findings and practical health-.care, diagnosis, and treatment outcomes. By highlighting real-care applications. It emphasizes the importance of translating scientific observations into meaningful improvements in patient world relevance, the study contributes to evidence based medical practice and supports informed clinical decision making. Ultimately, the findings aim to enhance patient quality of life, optimize therapeutic strategies, and promote better disease management in clinical settings.

ABBREVIATIONS

AR: Androgen receptor
DHT: Dihydrotestosterone
IL-6: Interleukin-6
IL-10: Interleukin-10
TNF-α: Tumor necrosis factor-alpha
STAT3: Signal transducer and activator of transcription 3
DHT: Dihydrotestosterone

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AUTHOR CONTRIBUTIONS

All authors significantly contributed to the study conception and design, data acquisition, or data analysis and interpretation. They participated in drafting the manuscript or critically revising it for important intellectual content, consented to its submission to the current journal, provided final approval for the version to be published, and accepted responsibility for all aspects of the work. Additionally, all authors meet the authorship criteria outlined by the International Committee of Medical Journal Editors (ICMJE) guidelines.

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CONFLICT OF INTEREST

Authors declared that there is no conflict of interest.

FUNDING

None

ETHICAL APPROVAL & CONSENT TO PARTICIPATE

All necessary consent & approval was obtained by authors.

CONSENT FOR PUBLICATION

All necessary consent for publication was obtained by authors.

DATA AVAILABILITY

All data generated and analyzed are included within this research article. The datasets utilized and/or analyzed in this study can be obtained from the corresponding author upon a reasonable request.

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The authors confirm that no AI & LLM tools were used in the writing or editing of the manuscript, and no images were altered or manipulated using AI & LLM.

AUTHOR'S NOTE

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REFERENCE

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