

Potential Anticancer, Anti-inflammatory, and Antioxidant Effects of Dutasteride on LNCap Prostate Cancer Cell Line

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Abstract

Background: Prostate cancer (PCa) is one of the main causes of death in men across the world. Particular focus has been placed on its preventative and treatment techniques, which include focusing on the activity of 5-alpha reductase enzyme which is responsible for the conversion of testosterone to dihydrotestosterone. These androgens are essential for prostatic development and function as well as for cells' proliferation and survival. **Objective:** The aim of this study was to evaluate the anti-proliferative, antioxidant, and anti-inflammatory effects of dutasteride alone or in combination with doxorubicin on the androgen-sensitive prostate cancer cell line LNCap. **Materials and Methods:** LNCap cells were incubated with dutasteride alone or combination of dutasteride with doxorubicin. MTT [3-(4,5 dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide] assay, caspase 3, tumor necrosis factor (TNF)-alpha, and total anti-oxidant capacity were assessed after 48h to evaluate anti-proliferative, apoptotic, anti-inflammatory, and anti-oxidant effects of dutasteride. **Results:** Dutasteride alone decreased cells viability and TNF-alpha and increased caspase 3 and total anti-oxidant capacity in LNCap cells. The combination of dutasteride with doxorubicin showed synergistic effects on cell viability, caspase 3, and TNF-alpha with no significant effects on total antioxidant capacity in LNCap cells. **Conclusion:** Dutasteride alone has anti-proliferative effects with apoptotic, anti-inflammatory and anti-oxidant effects on LNCap cells but when combined with doxorubicin the anti-oxidant effects of dutasteride decreased and other properties increased.

Keywords: 5-alpha reductase, anticancer activity, doxorubicin, dutasteride, LNCap, prostate cancer

INTRODUCTION

Prostate cancer is the second most frequent cancer and the fifth leading cause of cancer death among men worldwide with an estimated 1.4 million new cases and 375,000 deaths in 2020.^[1] There are many factors that associated with prostate cancer pathogenesis but the most important one is hormonal factors especially androgens. Androgens (testosterone and dihydrotestosterone) are essential for prostatic development and function as well as for cells' proliferation and survival.^[2] The most prevalent circulating androgen in males is testosterone (T), which is produced by the testicular Leydig cells under the direction of the hypothalamus and anterior pituitary gland.^[3] The microsomal enzyme 5-alpha reductase facilitates a quick and irreversible conversion of testosterone (T) to dihydrotestosterone (DHT) within the prostate gland. Then, DHT binds to the androgen receptor (AR), which

causes the expression of particular genes necessary for the growth of PCa cells.^[4]

In contrast, inflammation and oxidative stress are considered another type of factors that contributed in initiation and progression of prostate cancer. NF-B, a transcription factor that is primarily activated during inflammation by cytokines like tumor necrosis factor (TNF-), triggers one of the main inflammatory signaling pathways. Once active, this transcription factor controlled the synthesis of cytokines and proteins essential in the

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growth and spread of cancer.^[5] In contrast, the increased risk of prostate cancer has been linked to elevated levels of cellular reactive oxygen species (ROS) and compromised defensive systems.^[6] Oxidative free radicals are caused by several factors including regulating androgens, delaying the recruitment of p53, and inflammation. Specifically, it has been suggested that serum androgens increase ROS accumulation and production in prostate cancer cells.^[7]

The primary PCa treatments currently available include surgery, radiation therapy, chemotherapy, cryosurgery, and hormonal therapy.^[8] Dutasteride blocked both types (I and II) of 5-alpha reductase enzyme and may act as another form of treatment by targets the enzyme 5-alpha reductase that is responsible for converting testosterone to dihydrotestosterone since androgen levels, particularly in the early stages, play a crucial role in the growth of prostate cancer. In the 4-year Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, which is a randomized controlled trial, patients between the ages of 50 and 75 with prostate-specific antigen levels between 2.5 and 10.0ng/mL tested dutasteride for prostate cancer chemoprevention. Randomized trials employing dutasteride resulted in a about 25% reduction in the risk of prostate cancer.^[9] Another meta-analysis study on the impact of 5-alpha reductase inhibitors revealed that these drugs can slow the spread of prostate cancer overall, particularly in patients with localized disease and low Gleason scores of fewer than 7. Additionally, the progression-free survival time was extended, and the percentage of complete therapy responses increases.^[10]

Therefore, in resent study, we investigate the effects of dutasteride on proliferative rate of LNCap cells in addition to its anti-inflammatory and anti-oxidant effects on this type of cells in the presence of testosterone.

MATERIALS AND METHODS

Cells

Human prostate cancer (LNCap) cell line was obtained from Tissue Culture Laboratory in the College of Medicine, University of Babylon. The cells were cultured with phenol red free Roswell park memorial institute (RPMI) 1640 medium (Hi Media, Mumbai, India) containing 10% (v/v) fetal bovine (Capricorn, Germany) and 1% Penicillin-Streptomycin (Capricorn) at 37°C and passaged with Trypsin-EDTA (US Biological, Massachusetts, USA) every 3 days to maintain a cell monolayer. Dutasteride from (MedChem Express), testosterone from (Galenika, Serbian) and doxorubicin (Pfizer) were used in this study.

Cytotoxicity assay

Cell proliferation was evaluated using MTT (3-(4,5-Dimethylthiazole-2-yl)-2,5-diphenyl-2H-tetrazoliumbromide) (Roth, Germany). LNCap cells were cultured in 96 well plate in phenol-free RPMI 1640 supplemented with 10% fetal bovine serum and 1%

Penicillin-Streptomycin and incubated at 37°C for 24h. After incubation the medium was removed and LNCap cells were treated different concentrations of dutasteride (50, 25, 12.5, 6.25, 3.125, 1.5625) µg/mL in the presence of 7.8ng/mL of testosterone in the medium and incubated for 48 h. After incubation, 10 µL MTT solution was added to each well and incubated for 3 h. The mitochondrial reductase enzyme in viable cells converted the tetrazolium salts into a colored formazan product that is directly measured (at 570 nm) using an absorbance plate reader.

Next, LNCap cells were treated with different concentrations of doxorubicin (25, 12.5, 6.25, 3.125, 1.5625) µg/mL and incubate for 48 h. After incubation the MTT assay was performed as above to evaluate the cytotoxicity of doxorubicin.

In accordance with MTT results, the IC₅₀ for dutasteride and doxorubicin determined and was 75 µg/mL and 3 µg/mL, respectively. Then LNCap cells exposed to different concentrations of dutasteride combined with doxorubicin IC₅₀ (75:3, 37.5:3, 18.75:3, 9.375:3, 4.6875:3, 2.34:3) µg/mL for 48 h. After incubation, MTT assay was carried out.

Determination of caspase 3, tumor necrosis factor-alpha, and total antioxidant capacity

The apoptotic, anti-inflammatory, and anti-oxidant effects of dutasteride alone or with doxorubicin were assessed by using caspase 3, TNF-alpha, and total antioxidant capacity immunoassay Elisa kits (Elabscience).

Depending on MTT results, LNCap cells were incubated with different concentration dutasteride (50, 25, 6.25, 3.125), and different concentrations of dutasteride IC₅₀ combined with doxorubicin IC₅₀ (75:3, 18.75:3, 9.37:3) µg/mL and incubated for 48 h after incubation the levels of caspase 3, TNF-alpha, and total antioxidant capacity in supernatant were measured by using immunoassay ELISA kits according to manufacture protocol.

RESULTS

Effects of dutasteride, doxorubicin, and dutasteride combined with doxorubicin on proliferation rate of LNCap cells

LNCap cells were treated with dutasteride alone, doxorubicin alone, and dutasteride combined with doxorubicin for 48 h and then the proliferation rate was assessed by MTT assay. The results of dutasteride showed a highly significant ($P < 0.001$) decrease in cell viability at concentrations (50, 25, 12.5, 6.25, 3.125) µg/mL of dutasteride with significant ($P < 0.05$) decrease at concentration 1.5625 µg/mL compared to control group. Results are shown in Figure 1.

The results of doxorubicin in Figure 2 showed a highly significant ($P < 0.001$) decrease in cell viability at all concentrations of doxorubicin compared to control group, whereas the results of dutasteride combined with

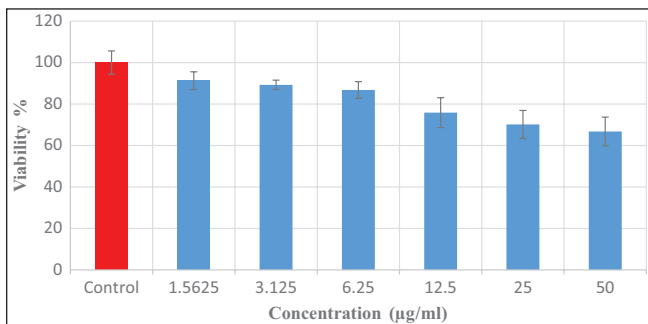


Figure 1: Effects of different concentrations of dutasteride on cell viability in LNCap cell line. Control: untreated cells

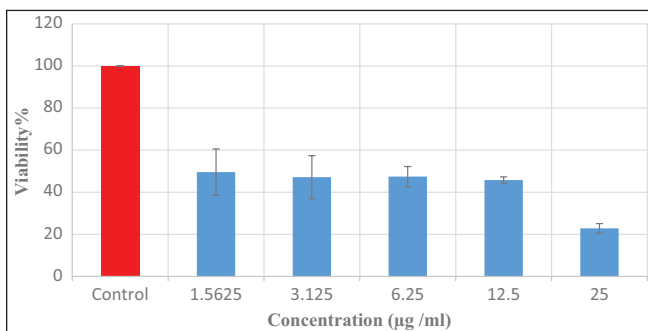


Figure 2: Effects of different concentrations of doxorubicin on cell viability in LNCap cell line. Control: untreated cells

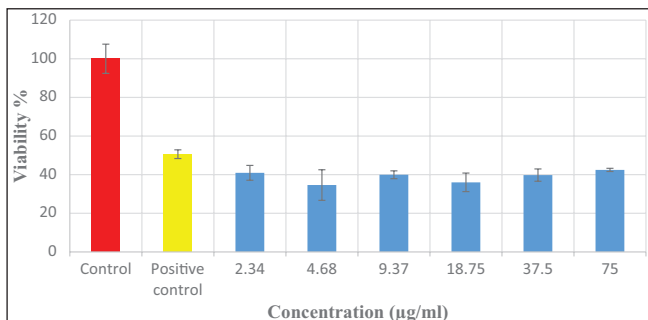


Figure 3: The effects of different concentrations of dutasteride in the presence of doxorubicin IC50 (3 µg/mL) on the viability of LNCap cell line. Control: untreated cells, Positive control: treated with doxorubicin (3 µg/mL)

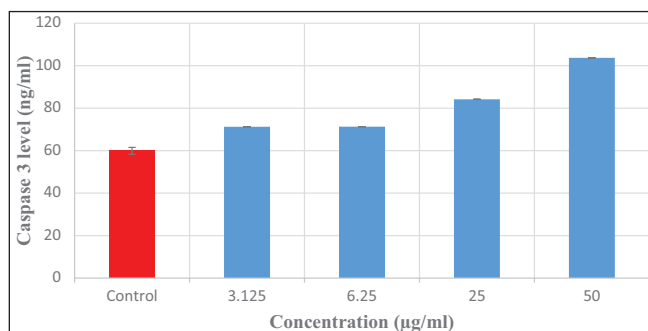


Figure 4: The effects of different concentrations of dutasteride on Caspase 3 levels in LNCap cell. Control: untreated cells

doxorubicin in Figure 3 showed a highly significant ($P < 0.001$) decrease in cell viability at all concentrations compared to positive control group (3 µg/mL).

Apoptotic effects of dutasteride alone or combined with doxorubicin on LNCap cells

The results of dutasteride alone or in combination with doxorubicin showed a highly significant ($P < 0.001$) increase in caspase 3 levels at all concentrations compared to control group [Figure 4 and 5].

Effects of dutasteride alone or combined with doxorubicin on tumor necrosis factor-alpha in LNCap cells

Results of dutasteride revealed a highly significant ($p < 0.001$) decrease in TNF-alpha at all concentrations compared to control group [Figure 6]. Dutasteride combined with doxorubicin also showed a highly significant ($P < 0.001$) decrease in TNF-alpha at all concentrations compared to positive control group (3 µg/mL) as shown in Figure 7.

Effects dutasteride alone or combined with doxorubicin on total anti-oxidant capacity in LNCap cells

The results of dutasteride revealed a highly significant ($P < 0.001$) increase in total antioxidant capacity (TAC)

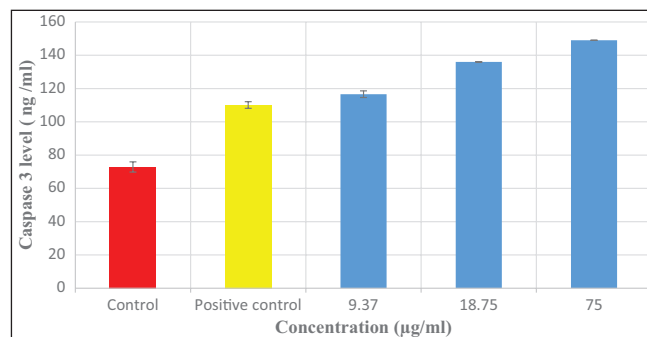


Figure 5: The effects of different concentrations of dutasteride in the presence of doxorubicin IC50 (3 µg/mL) on caspase 3 levels in LNCap cell line. Control: untreated cells, Positive control: treated with doxorubicin (3 µg/mL)

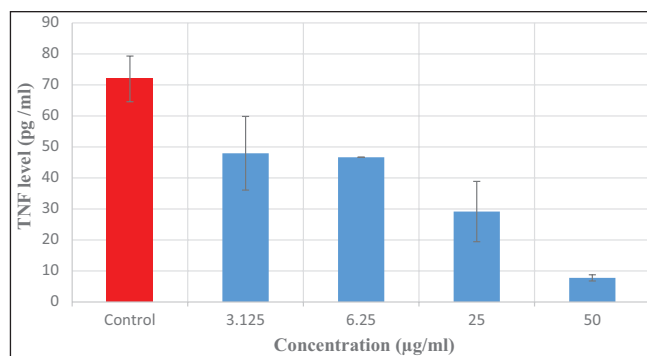


Figure 6: The effects of different concentrations of dutasteride on TNF-alpha levels in LNCap cell line. Control: untreated cells

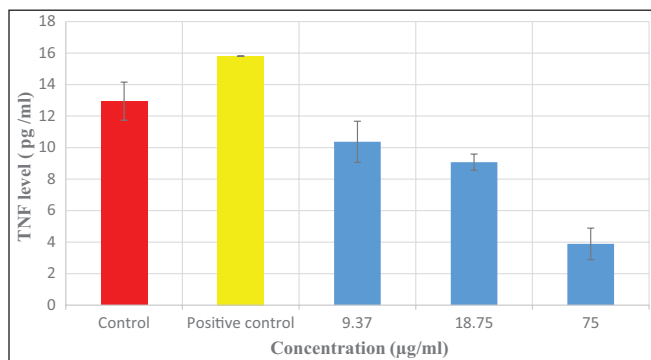


Figure 7: The effect of different concentrations of dutasteride in the presence of doxorubicin IC50 (3 µg/mL) on TNF-levels in LNCap cell line. Control: untreated cells, Positive control: treated with doxorubicin (3 µg/mL)

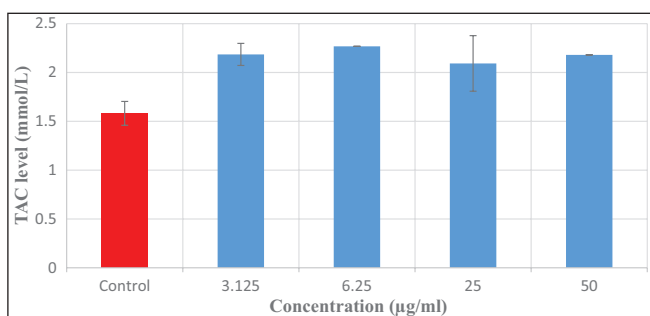


Figure 8: The effects of different concentrations of dutasteride on total antioxidant capacity (TAC) levels in LNCap cells. Control: untreated cells

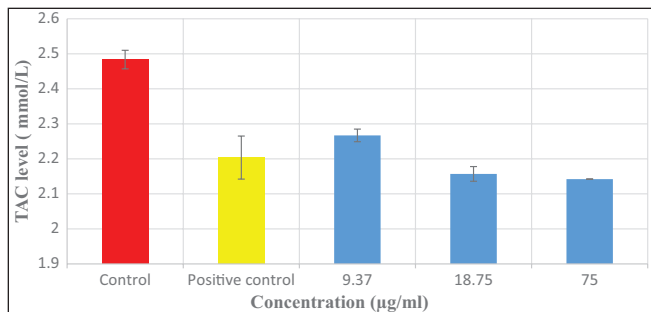


Figure 9: The effects of different concentrations of dutasteride in the presence of doxorubicin IC50 (3 µg/mL) on total antioxidant capacity (TAC) levels in LNCap cell line. Control: untreated cells, Positive control: treated with doxorubicin (3 µg/mL)

at all concentrations of dutasteride compared to control group. Results are shown in Figure 8, whereas the results of dutasteride combined with doxorubicin in Figure 9 showed no significant differences on TAC level at all concentrations compared to positive control group (3 µg/mL)

DISCUSSION

Lazier *et al.*^[11] had shown that dutasteride can inhibit the conversion of testosterone to dihydrotestosterone by more than 99% in LNCap cells by blocking both types of 5 alpha reductase enzyme which already present in LNCap

cells.^[12] To confirm this effect, we incubated the LNCap cells with different concentrations of dutasteride for 48h in the presence of constant concentration of testosterone. After the incubation the effects of dutasteride on cell viability was assessed by MTT assay. The results showed a dose dependent inhibition of cell viability with highly significant decreasing at high concentrations. This results can have explained depending on the ability of dutasteride to inhibit 5 alpha reductase enzyme and prevent the conversion of testosterone to dihydrotestosterone which is considered the main and powerful androgen that could regulate the growth and survival of prostate cells. This results and explanation were agreed with study of Schmidt *et al.*^[13] In this study LNCap was exposed to different concentrations of dutasteride and the inhibition was noted after 48h in the presence of DHT. Schmidt *et al.* in their study showed that dutasteride was capable of inhibiting the proliferation of LNCap not only by preventing T to becoming DHT but also dutasteride was capable of up-regulating two genes, UGT2B15 and UGT2B17. These UDP-glucuronosyltransferases can inactivate the DHT or its metabolites and this may be considered another mechanism by which dutasteride was inhibited by the proliferation of cells and this effects were consistent with our results because dutasteride was able to inhibit the proliferation of cells in spite of the presence of testosterone in media. Also these effects are consistent with Lazier *et al.*^[11] study where the proliferation rate of LNCap cells was still dramatically decreased after exposure to dutasteride combined with exogenous DHT. Depending on these results, dutasteride may have a benefit in prostate cancer especially in earlier stages when cancer is still sensitive to androgens.

To investigate whether dutasteride lowered the cell viability due to apoptotic pathway, we exposed the LNCap cells to different concentrations of dutasteride and incubated for 48h. After incubation the level of caspase 3 (one of the most crucial caspases in the apoptosis pathways) was measured in the supernatant to assess the apoptotic effects of dutasteride. The results showed highly significant increase in caspase 3 at all concentrations of dutasteride. This indicated the dutasteride may interfered with apoptotic pathways of LNCap cells and leading to caspase 3 elevation. These results may have resemblance with Golbano *et al.*^[14] study who used finasteride which is another 5 alpha reductase inhibitor and also blocks both types of enzyme but with more selectivity to type 1. LNCap cells in this study were incubated with different concentrations of finasteride for 4 days. After incubation the procaspase 3 (which is inactive form of caspase 3 and converted to caspase 3 after proteolytic activation) was measured. Finasteride showed a significant decrease in procaspase 3 (which means caspase 3 increasing). Therefore, finasteride induces apoptosis in LNCap cells by activating caspases. Also finasteride showed a

significant descent in the expression of the anti-apoptotic proteins Bcl-2 and Bcl-xL with significant increasing in the expression of pro apoptotic proteins Bax ratios, and this may indicate that finasteride may increase caspase3 due to intrinsic pathway of apoptosis.^[14] As per our study, dutasteride showed a significant increase in caspase 3 only after 48 hr. We suggest that dutasteride may increase caspase 3 in mechanism similar to finasteride but with less time less than finasteride do because dutasteride was considered more potent and highly selective to both types of 5 alpha reductases than finasteride.

Likewise, anti-proliferative and apoptotic effects of dutasteride were increased significantly when combined with doxorubicin. Doxorubicin and other anthracyclines primarily work by inducing a DNA damage response, which then initiates an apoptotic pathway to destroy proliferating cells like cancer cells. Lin *et al.*^[15] showed in their study that doxorubicin caused p53 overexpression in LNCap cells. In general, when DNA is exposed to any type of damage the p53 will get activated and try to repair this damage. If repairing process failed, the p53 will trigger the cell to apoptosis by activating intrinsic apoptotic mechanism that could lead to the activation of caspase cascades which eventually activate caspase 3 and induce cell death. Other study by Yang *et al.* evaluated the apoptotic response to doxorubicin between LNCap and PC3 cells. As the minimal dose of doxorubicin is required to activate caspase 3, the outcomes showed that doxorubicin promotes apoptosis in LNCap cells at very low concentrations. In PC3 cells, doxorubicin can similarly activate caspase 3, but it does so at a 4- to 8-fold greater dose than it can in LNCap. They were informed that Bcl-xl, an anti-apoptotic protein, is present in PC3 cells at a level that is around five times greater than that of LNCap cells. And the primary distinction between the two cells was this elevation. Additionally, they demonstrated that the sole protein capable of inhibiting Bcl-xl activity in response to doxorubicin-induced apoptosis in LNCap cells is Bim (pro-apoptotic protein).^[16] Depending on these studies, dutasteride (which also increased caspase 3 in LNCap by mechanisms showed above) was combined with doxorubicin and give synergistic effects on LNCap cells.

Some studies showed that TNF-alpha has been increased in PCa patients.^[17] Likewise, Pro-inflammatory cytokines (especially TNF-alpha) levels were correlated with prostate cancer. TNF-alpha may be connected to disease progression, with levels being lowest in men with good health, greatest in individuals with bulky locally advanced PCa, and highest in those with metastatic disease, according to some research.^[18] TNF was found to inhibit DHT-induced proliferation of LNCap cells and to dose-dependently reduce the expression of the AR, suggesting that TNF may play a role in the beginning of an androgen-independent state in these cells.^[19] After making an analysis on these studies, we suggested that

any drug may have role in decreasing of TNF-alpha may contribute in reducing or even limiting the progression and initiation of prostate cancer. In this study we tested the anti-inflammatory effects of dutasteride which is one of 5 alpha reductase inhibitors on LNCap cell line. The cells were exposed to different concentrations of dutasteride and incubated for 48 hrs. After incubation the levels of TNF-alpha were measured. The results showed a highly significant decreasing in TNF levels at all concentrations of dutasteride. This indicated that dutasteride will have anti-inflammatory effects on LNCap by reducing TNF levels. The definitive mechanism by which dutasteride has lowered the TNF-alpha was unclear in other studies and the recent study was the first study that examined dutasteride as anti-inflammatory effects on LNCap cells. But considering the study of Zhao *et al.* we explained this effect. In their study, they made a surgical prostatic wound in experimental canines and focused on effects of androgens and inflammation in the presence finasteride. They found after 1-2 weeks the macrophages and concentration of TNF-alpha in testosterone group more than finasteride group at the site of wound. Also after adding small dose of DHT the TNF-alpha was increased. They explained that DHT can upregulate the TNF-alpha during activation AR on activated macrophage.^[20] Therefore, as per these results, DHT may act on AR that is present in LNCap cells and increase TNF-alpha from cells (as we know TNF-alpha is released from cancer cells' macrophages and other cells of immune system). Therefore, blocking 5 alpha reductase enzyme by dutasteride and reducing DHT in prostate may contribute in decreasing the level of TNF which is considered one of the important activators of NF- κ B pathway that already activated in cancer cells. Also these results were confirmed by^[21] who found subcutaneous testosterone administration in mice was activated NF- κ B pathway in prostate cells and the levels of TNF with other cytokines were elevated. On the other hand, several studies demonstrated that chemotherapy activated p38 mitogen-activated protein kinase (p38 MAPK) in cells. Activation of p38 MAPK-mediated release of proinflammatory cytokines which are associated with fatigue similar to sickness behavior that occurs during chemotherapy uses.^[22] Also chemotherapy can activate p38 MAPK in tumor cells as a part of its cytotoxic activity on these cells.^[23] Elsea *et al.*^[24] showed that doxorubicin and other chemotherapies activate p38 MAPK in model cell systems. And this activation was associated with increasing IL-6, TNF-alpha and other cytokines. On the other hand, inhibition of p38 MAPK caused IL-6, TNF-alpha, and other cytokines lowering without effecting on cytotoxic effects of chemotherapies. In accordance with these studies, we can suggest that doxorubicin may activate p38 MAPK in LNCap as a part of its cytotoxic effects and result in TNF-alpha elevation. But when combined with dutasteride which showed anti-inflammatory effects during this study by decreasing

TNF-alpha, this resulted in decreasing of inflammatory effects of doxorubicin in dose-dependent manner without showing an effect on doxorubicin cytotoxicity (caspase 3 was high and cell viability was low). Therefore, combination of dutasteride with doxorubicin might contribute in the decrease the inflammatory effects of doxorubicin and further investigations should applied to confirm these effects.

Previous studies have been shown that one of important factors that contributed in progression and initiation of prostate cancer is oxidative stress (OS).^[25] On the other hand, some researches explained that molecules such as antioxidants can protect prostate cells against OS and play an important role in PCa prevention.^[26] Likewise, many therapies may possess antioxidant properties or cause oxidative stress in cancer cells. In a recent study, we evaluated the effects of dutasteride on oxidative stress by measuring TAC in supernatant of LNCap cell line. We exposed LNCap to different concentrations of dutasteride and incubated for 48 h. After incubation the TAC was measured. The results showed a highly significant increase in TAC at all concentrations compared with control. This result means that dutasteride may have antioxidant activity in these cells. No previous studies showed these effects of dutasteride on this type of cells. But study of Ripple *et al.* showed that physiologic androgen levels can increase oxidative stress in androgen-responsive LNCap prostate cancer cells. According to the data, this effect is attributed in part to enhanced mitochondrial activity. Androgens also affect intracellular glutathione levels as well as the activity of detoxifying enzymes like gamma-glutamyl transpeptidase, which are critical for maintaining the cellular prooxidant-antioxidant equilibrium.^[27] Depending on this study we can predict that dutasteride may reverse these effects of androgens in LNCap by blocking the 5 alpha reductase enzyme and prevent the conversion of T to DHT which is leading to reduce intraprostatic DHT and decreasing its oxidative stress-inducing effects. On the other hand, certain reports have shown that anthracycline anti-cancer medications may increase the amount of hydrogen peroxide produced inside of cells. Doxorubicin's conversion to a semiquinone by metabolic reductive activation increases the one-electron reduction of oxygen to produce superoxide. Superoxide dismutase enzymes or spontaneous dismutation of the resultant superoxide produces H₂O₂, which may be the species causing the cytotoxicity of doxorubicin.^[28] Also in the study of Wagner *et al.*^[29] they demonstrated an increase in intracellular hydrogen peroxide as a particular oxidative event related to anthracycline exposure in PC3 human prostate cancer cells. These results concur with our study, in which doxorubicin (positive control) showed a decrease in TAC level compared with negative control; this is due to the ability of doxorubicin to produce free radicals inside cells. Also recent studies showed that cardiotoxicity

that is associated with doxorubicin was resulted from doxorubicin ability to produce free radicals.^[30] During our study, combination of dutasteride (which was shown a highly anti-oxidant activity by increasing TAC level) with doxorubicin did not show any significant effects on oxidative effects of doxorubicin. In contrast, combination of doxorubicin with dutasteride can decrease the anti-oxidant effects of doxorubicin when we compared with negative control. This may have indicated that doxorubicin is a potent oxidative agent and this makes it a potent anticancer agent. Therefore, dutasteride may decrease the cytotoxic effects of doxorubicin on other normal cells without affecting on cytotoxic effects on cancer cells. Further investigations are needed to confirm these effects.

CONCLUSION

Dutasteride alone has antiproliferative, apoptotic, anti-inflammatory, and anti-oxidant effects on LNCap cells by reducing cell viability, increasing caspase 3, decreasing TNF-alpha and increasing total anti-oxidant capacity. Combination of dutasteride with doxorubicin gives synergistic effects on cell viability, as well apoptotic and anti-inflammatory properties with no effects on anti-oxidant capacity.

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Conflicts of interest

There are no conflicts of interest.

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