γ-Tocotrienol inhibition of androgen receptor (AR) expression and activation in triple-negative breast cancer (TNBC) MDA-MB-231 and MDA-MB-453 cells is associated with a reduction in cellular proliferation

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Introduction

Breast Cancer:

Breast cancer can be defined as malignant neoplasm of the breast arising from the epithelial lining of the lobule, ducts and the nipple. Symptoms of breast cancer include a lump in the breast, bloody discharge from the nipple, and changes in the shape or texture of the nipple or breast.

Triple-Negative Breast Cancer:

Triple-negative breast cancer (TNBC) is an aggressive invasive malignancy with the lowest 5-years survival rate. In TNBC estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER-2) are not present in the cancer tumor. As there is no receptor targets for chemotherapy drugs is available in TNBC, cancer cells may not stop growing with chemotherapy treatment. TNBC occurs in about 15-20% of diagnosed breast cancers and is more likely to affect younger people, African Americans, Hispanics, and/or those with a BRCA1 gene mutation.

Role of Androgen Receptor in Breast Cancer:

Gene expression profiling indicates that TNBC is a heterogeneous disease and at present, there is no targeted therapy available for treatment. Approximately one-third of TNBC expressed androgen receptor (AR) and evaluation of AR-positive TNBC primary tumors shows nuclear localization of AR, an indication of transcriptionally active receptors. Activation of AR play roles in cell proliferation, survival and differentiation.

Role of Androgen Receptor in Breast Cancer:

Previous studies have shown that AR inhibition or AR knockdown significantly reduces baseline proliferation, anchorage-independent growth, migration and invasion and increase apoptosis in different TNBC cell lines. AR levels are most abundant in the luminal AR (LAR) molecular subtype of TNBC, but other non-LAR molecular TNBC subtypes also display AR expression and activity.

γ-Tocotrienol:

Different isomers of vitamin E includes tocopherols & tocotrienols. Tocotrienols display potent anti-cancer effects. In our lab we conduct research on the anti-cancer effects of γ-tocotrienol which is a rare natural isoform of vitamin E. γ-Tocotrienol displays potent anti-proliferative and apoptotic activity in different breast cancer cell lines such as +SA, MCF7, MDA-MB-231, MDA-MB-453 & BT474 cell lines.

Aims of the Study:

To determine the effect of γ-tocotrienol treatment on cellular proliferation, migration and epithelial to mesenchymal transition (EMT) in MDA-MB-231 and MDA-MB-453 TNBC cell lines.

Analytical Methods:

MTT assay, Western Blot, confocal microscopy, wound healing assay, and transwell invasion assay.

Results

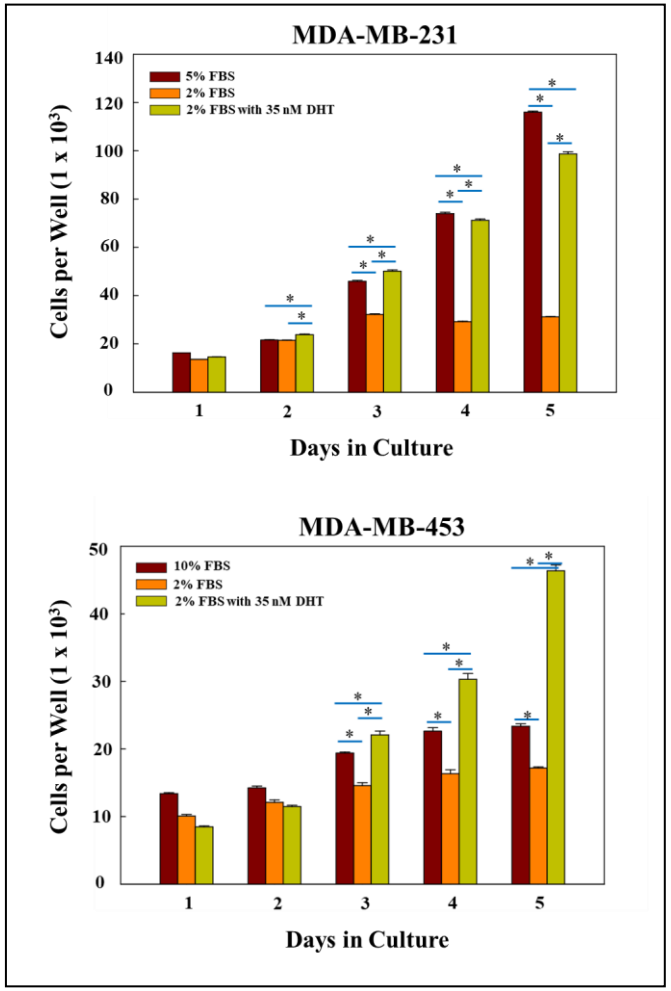

Figure 1: 35 nM Dihydrotestosterone (DHT) induced AR mediated proliferation in MDA-MB-231 & MDA-MB-453 cells.

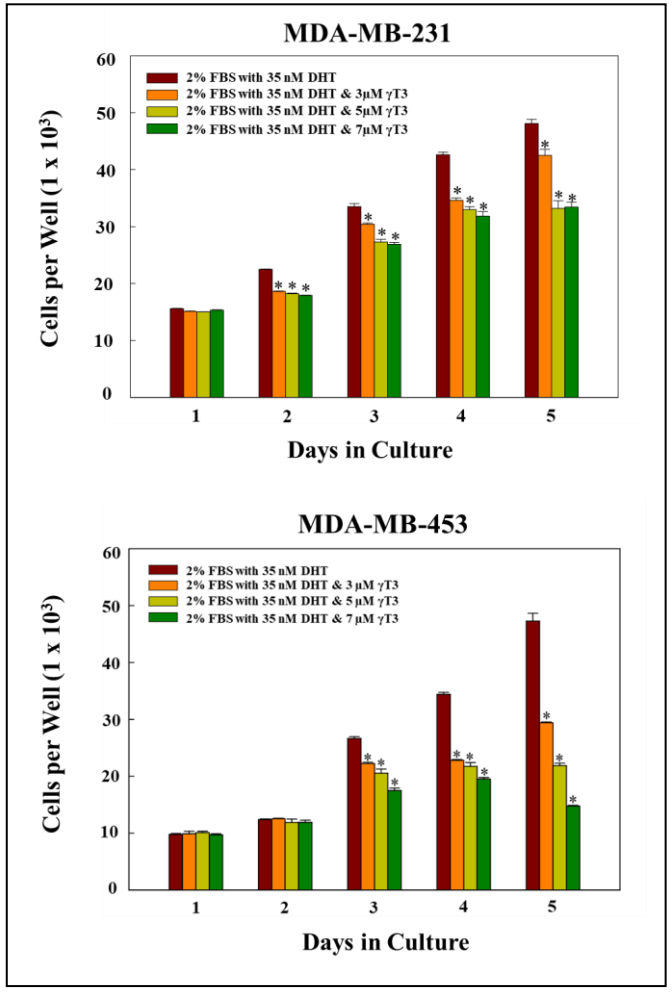

Figure 2: γ-Tocotrienol (3 μM, 5 μM & 7 μM) significantly inhibits DHT-induced proliferation in MDA-MB-231 & MDA-MB-453 cells.

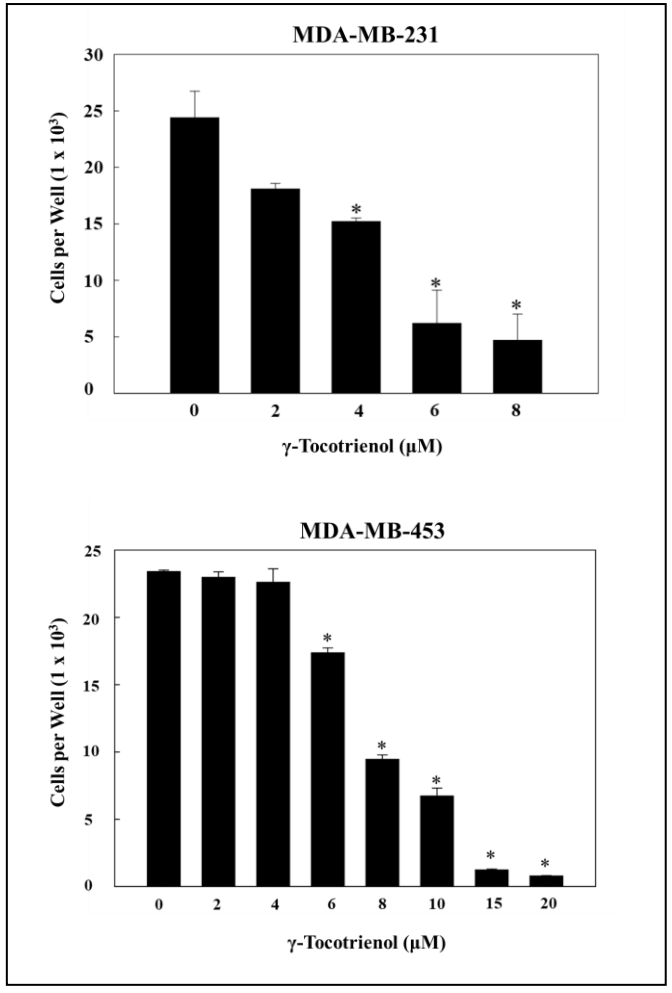

Figure 3: γ-Tocotrienol inhibits cell viability in human MDA-MB-231 & MDA-MB-453 breast cancer cells. IC50 for MDA-MB-231 is 5 μM and for MDA-MB-453 is 7 μM.

Results

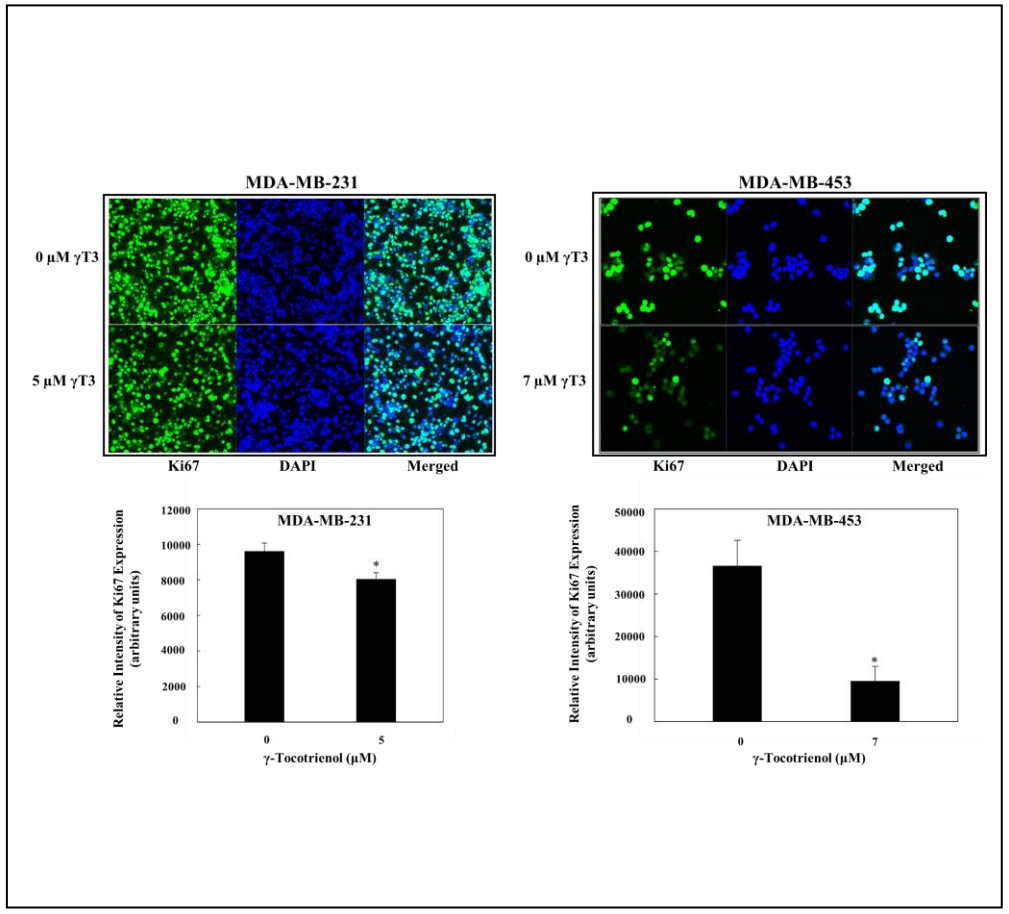

Figure 4: γ-Tocotrienol inhibits Ki67 expression in human MDA-MB-231 & MDA-MB-453 breast cancer cells.

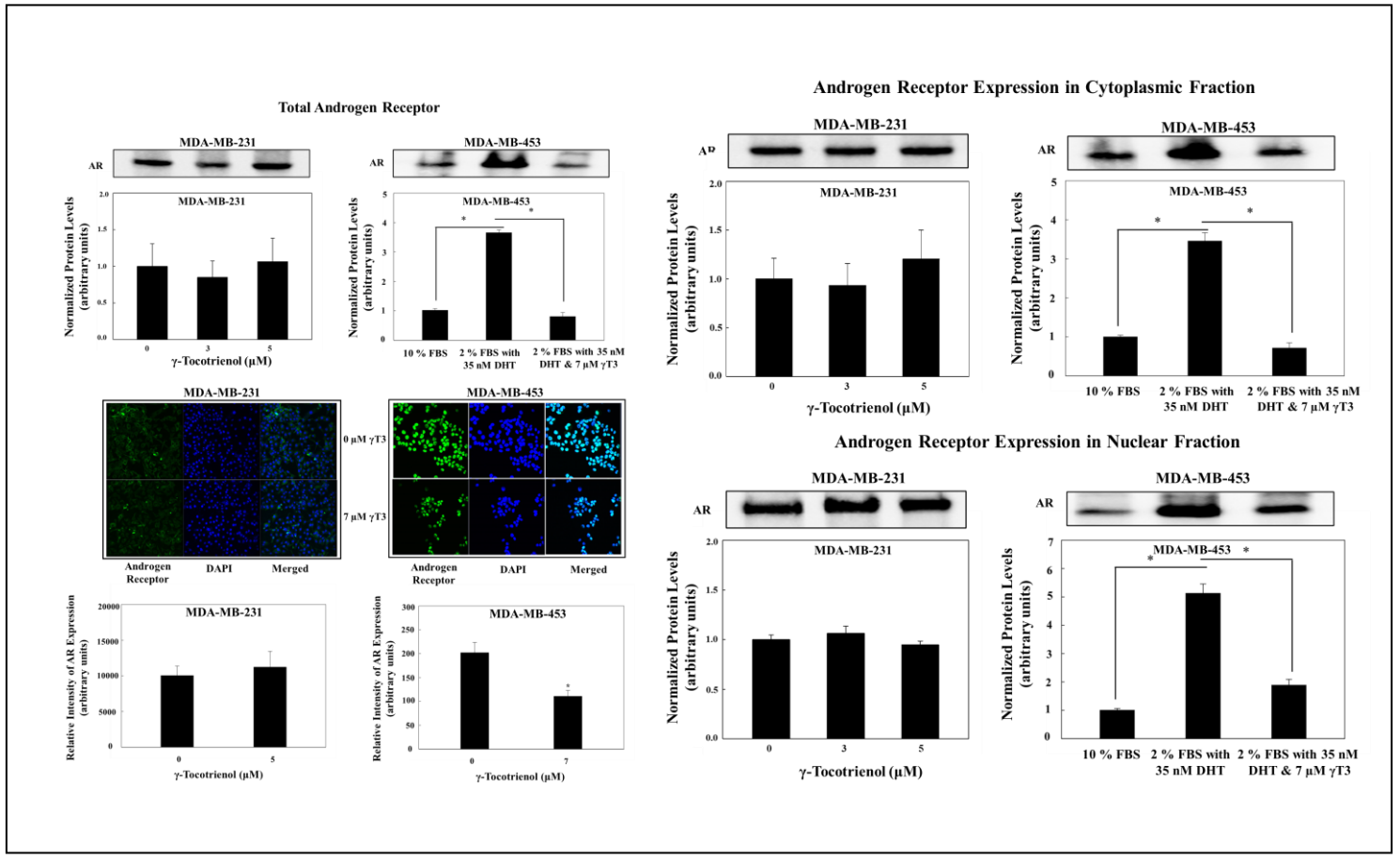

Figure 5: Effects of γ-tocotrienol on androgen receptor (AR) expression in MDA-MB-231 & MDA-MB-453 breast cancer cells.

Results

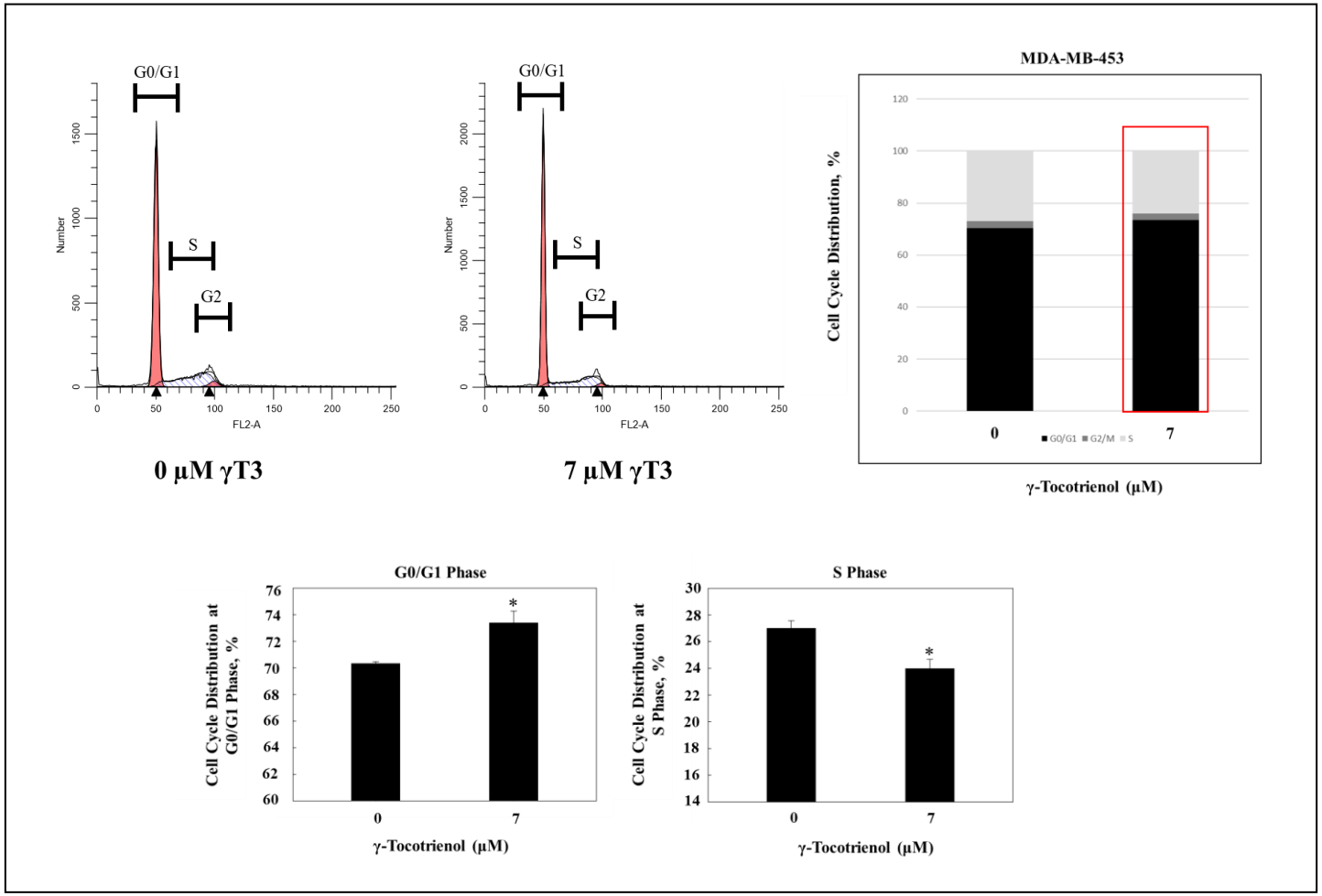

Figure 6: Effect of γ-tocotrienol on cell cycle progression in MDA-MB-453 breast cancer cells.

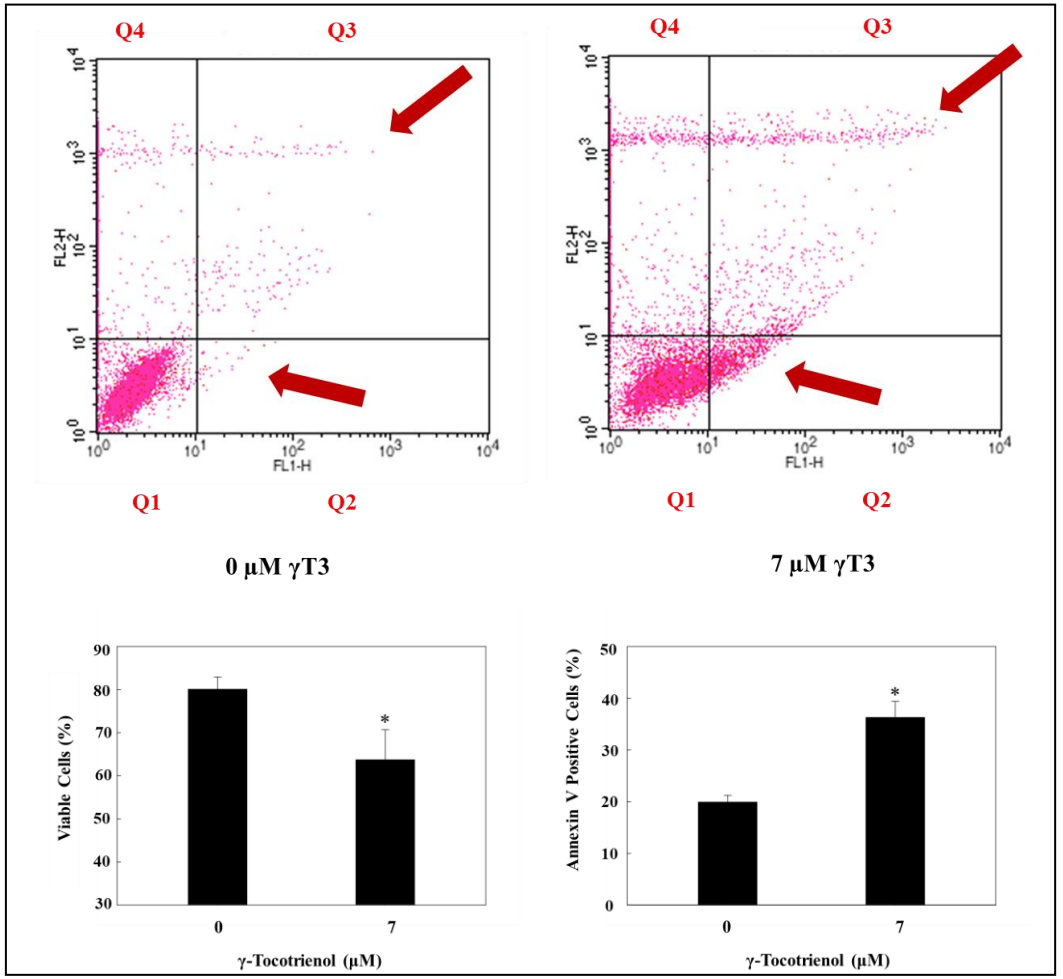

Figure 7: Effect of γ-tocotrienol treatment on apoptosis in MDA-MB-453 breast cancer cells.

Results

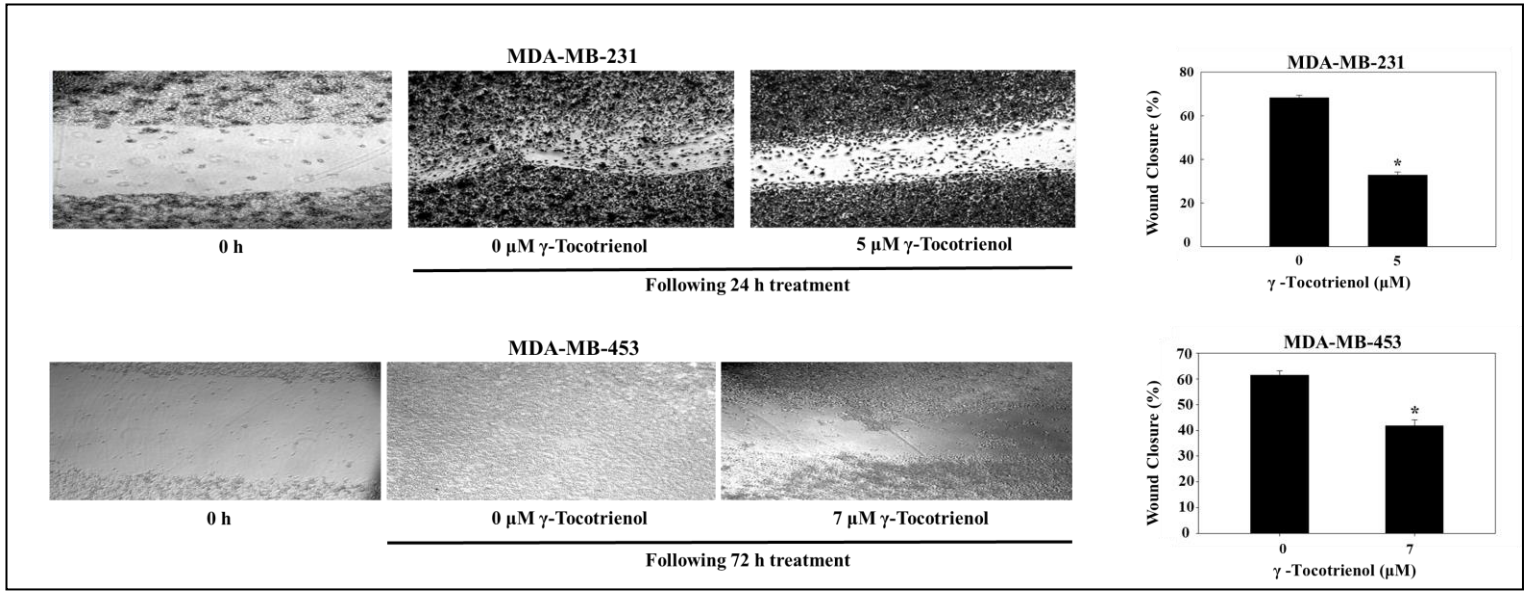

Figure 8: γ-Tocotrienol inhibits human triple-negative breast cancer cells migration.

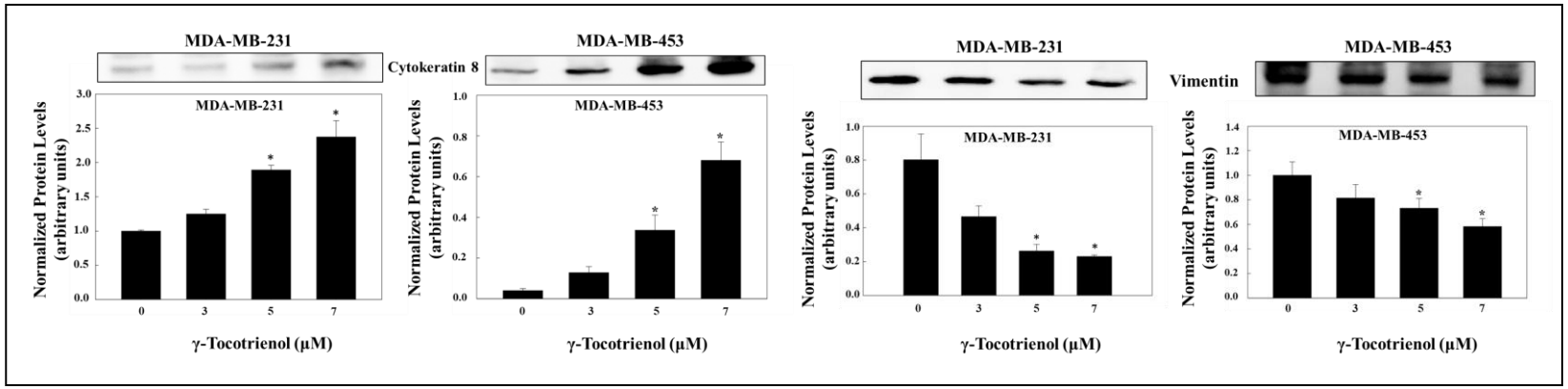

Figure 10: Effect of γ-tocotrienol treatment on EMT markers in MDA-MB-231 & MDA-MB-453 breast cancer cells.

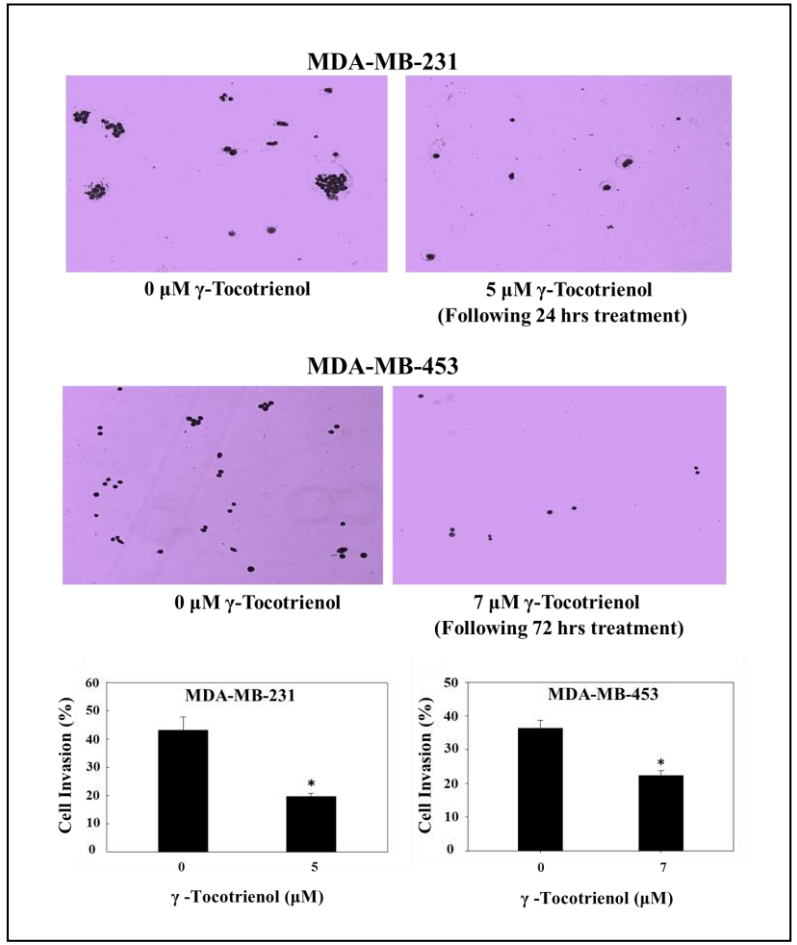

Figure 9: γ-Tocotrienol inhibits MDA-MB-231 & MDA-MB-453 breast cancer cells invasion.

Conclusion:

- γ-Tocotrienol treatment inhibits AR expression as well as DHT-dependent cell proliferation, migration and EMT in TNBC.

- These findings also suggest that AR may be a potential therapeutic target for the treatment of both LAR and non-LAR TNBC subtypes.

Acknowledgment:

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