**Abstract form**

Mechanistic Insights into Melittin’s Efficacy Against Tamoxifen-Resistant Breast Cancer: Apoptosis, Proliferation, and Migration Modulation

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**Purpose**

Tamoxifen is a standard treatment for hormone receptor-positive breast cancer in premenopausal women, while aromatase inhibitors (AIs) are used for postmenopausal patients. Understanding resistance mechanisms through relevant models is essential for discovering new treatments. Our previous study found that melittin, a compound derived from bee venom, significantly inhibits the effects of tamoxifen, AIs, trastuzumab, and multidrug-resistant human breast cancer cell lines. This inhibition was particularly notable in tamoxifen-resistant MCF-7 cells (MCF7/TamR-8) and AI-resistant cell lines. This study aims to explore the potential of melittin to overcome endocrine resistance by further investigating and comparing its mechanisms of action in tamoxifen-resistant and AI-resistant cell lines.

**Materials and Methods**

MCF7/TamR-8 cells, a tamoxifen-resistant subline, and three AI-resistant sublines of MCF7 cells were treated with melittin under indicated conditions. The effects on apoptosis, cell proliferation, and migration were assessed. Potential pathways regulated by melittin were analyzed using western blotting.

**Results**

After 24 hours of melittin treatment, significant damage to the cell membrane was observed in MCF7/TamR-8 cells, with effects more pronounced than in AI-resistant cell lines. Melittin treatment notably inhibited cell proliferation and induced apoptosis at concentrations greater than 0.5 µM, which was associated with the down-regulation of PCNA expression. In wound healing assays, melittin treatment reduced cell migration in MCF7/TamR-8 cells, with inhibition becoming more pronounced over time. Additionally, melittin also regulated endothelial-to-mesenchymal transition by suppressing the expression of N-cadherin, Slug, and vimentin, and downregulated mitogen-activated protein kinase (MAPK) signaling in MCF7/TamR-8 cells.

**Conclusion**

Melittin effectively targets tamoxifen-resistant breast cancer cells by inducing apoptosis, inhibiting cell proliferation, and reducing migration. These effects were less pronounced in AI-resistant cell lines, suggesting selective cytotoxicity of melittin towards tamoxifen-resistant breast cancer cells. The results underscore melittin’s potential as a therapeutic agent for endocrine-resistant breast cancer and warrant further investigation.