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Dimethyl itaconate attenuates ovarian histological changes and apoptosis, and improves sex hormone production in doxorubicin-treated 4T1 breast cancer mice

Azam Asad-Saftjani[1], Shima Hosseinifar[2*] and Mohammad Reza Tabandeh[3]

[1] PhD Student of Histology, Faculty of Veterinary Medicine, Shahid Chamran University of Ahvaz, Ahvaz, Iran
[2] Associate Professor, Department of Basic Sciences, Faculty of Veterinary Medicine, Shahid Chamran University of Ahvaz, Ahvaz, Iran
[3] Professor, Department of Basic Sciences, Faculty of Veterinary Medicine, Shahid Chamran University of Ahvaz, Ahvaz, Iran and Professor, Stem Cells and Transgenic Technology Research Center, Shahid Chamran University of Ahvaz, Ahvaz, Iran

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Abstract

Ovarian toxicity induced by Doxorubicin (DOX) is a common side effect treatment in breast cancer, leading to apoptosis, impaired folliculogenesis and reduced ovarian steroid hormone levels. Dimethyl itaconate (DMI) is an immunometabolite with anti-inflammatory and antioxidant properties that could play a protective role, although data are limited. This study evaluated the potential protective effects of DMI on ovarian histology, apoptosis, and ovarian hormone production in a 4T1 breast cancer mouse model treated with DOX. In this study, 30 adult female BALB/c mice were randomly divided into five groups: healthy control, cancer control (cancer induction by injection of 4T1 cells), cancer - DMI (50 mg/kg; daily; IP, 28 days), cancer - DOX (5 mg/kg; once a week; IP, 4 weeks) and DMI + DOX cancer. Serum estrogen and progesterone levels, ovarian apoptotic gene expression (Bax and Bcl2), and histological changes were evaluated. Statistical analysis was performed by GraphPad Prism software (10) and data were presented as mean ± standard deviation. DOX significantly decreased estradiol (E2; 37.23 ± 4.43 pg/ml) and progesterone (P4; 3.4 ± 0.2 ng/ml) levels, reduced Bcl2 (0.31 ± 0.1) expression and increased Bax expression (4.04 ± 0.39) in ovarian tissue compared to cancer control group (54.10 ± 2.8 pg/ml, 5.1 ± 0.2 ng/ml; 0.72 ± 0.09; 1.81 ± 0.35, respectively). Co-treatment with DMI and DOX led to a significant decrease in Bax expression (2.59 ± 0.45) and a significant increase in Bcl-2 (0.61 ± 0.03) expression compared to the only DOX treated cancer group. DOX caused notable ovarian damage, including increased follicular atresia, reduced follicle size, and absence of corpus luteum. DMI treatment mitigated these effects by preserving ovarian architecture, thinning the surface epithelium, and normalizing hormone levels and expression of apoptosis-related genes. Co-administration of DMI and DOX was particularly effective in reducing DOX-induced histological damage. These findings suggest that DMI may serve as a potential protective compound for reducing DOX-induced ovarian toxicity during chemotherapy.

Key words: Dimethyl Itaconate, Doxorubicin, Ovarian histology, Apoptosis, Breast cancer

[*] **Corresponding Author**: Shima Hosseinifar, Associate Professor, Department of Basic Sciences, Faculty of Veterinary Medicine, Shahid Chamran University of Ahvaz, Ahvaz, Iran
E-mail: sh.hosseinifar@suc.ac.ir

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