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Transcriptomic Profiling Reveals Marein-Mediated Modulation of Inflammatory Pathways in Doxorubicin-Induced Cardiotoxicity

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Doxorubicin (DOX) is a potent chemotherapeutic agent whose clinical utility is limited by dose-dependent cardiotoxicity (DICT). Understanding the molecular signatures of DICT is essential for developing strategies to reduce cardiac injury. Marein, a flavonoid from Coreopsis tinctoria, exhibits antioxidant and anti-inflammatory properties, but its global transcriptomic effects under DOX exposure have not been systematically characterized.

To address this, we combined in vitro (H9c2 rat cardiomyoblasts, human cardiomyocytes) and in vivo (C57BL/6 mice) models with transcriptome-wide RNA sequencing to evaluate marein's effects on DOX-induced gene expression. Differentially expressed genes (DEGs) were identified and analyzed by enrichment analysis. Functional validation included assessment of cell viability, apoptosis (cleaved caspase-3, caspase-9, PARP, Bcl-xL), and MAPK pathway phosphorylation. In vivo cardiac function was evaluated using electrocardiography and serum biomarkers.

Marein treatment restored cardiomyocyte viability, decreased ROS production, inhibited apoptosis, and improved cardiac functional parameters, while preserving the anticancer activity of DOX in MDA-MB-231 cells. Transcriptomic profiling identified 1,576 DEGs regulated by marein, with gene set enrichment analysis indicating reversal of DOX-induced inflammatory and interferon-γ response pathways. qRT-PCR confirmed regulation of IL6, IRF4, CCL5, VCAM1, and TNFAIP3.

Together, these findings demonstrate that marein mitigates DOX-induced cardiotoxicity by remodeling inflammatory signaling and apoptotic pathways without compromising chemotherapeutic efficacy. This work provides a systems-level resource for understanding natural compound–mediated cardioprotection and establishes a data-driven foundation for future computational modeling and AI-assisted prediction of drug–host interactions.