A Model for Reversing the Cardiotoxic Effects of Doxorubicin via Fisetin in Saccharomyces cerevisiae

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Doxorubicin is a globally utilized drug for cancer treatment. This drug has unfortunate cardiotoxic side-effects through drug-induced functional loss of iron-regulatory proteins (IRP1, IRP2), enabling iron dysregulation within the cell. Doxorubicin-induced toxicity leads to downstream events, such as the overaccumulation of intracellular iron, hydroxyl radical formation through the Fenton Reaction, and caspase-9 activation, leading to cardiomyocyte apoptosis. This study aims to reverse the effects of iron overload in a eukaryotic cell model using the natural compound fisetin. Wild-type Saccharomyces cerevisiae (brewers yeast), propagated through fermentation on malt-agar, was treated with ferrous sulfate to induce iron toxicity via the Fenton Reaction. A cell viability analysis, using methylene blue as an indicator, was conducted with over 10,000 cells via a hemocytometer. Results showed that 62.8% of the ferrous sulfate-treated yeast cells died. Following fisetin treatment, in ferrous sulfate pre-treated yeast, this cell death percentage diminished to 37.4% of cells dead, 0.8% less than the control cell mortality. Statistical significance was established for the cell-death percentages across the three samples. 150 molecular docking simulations were performed and analyzed to support fisetin's ability to inhibit caspase-9, a key apoptosis regulator. Fisetin showed strong inhibition potency, with an 8.86-micromolar inhibition constant for caspase-9. A novel finding was that fisetin is bound to exosite F of caspase-9, supporting its ability to block the active site of caspase-9 and inhibit cell death. This data supports future studies investigating fisetin-mediated inhibition of doxorubicin-induced iron toxicity in multicellular organisms to make cancer treatment safer.

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