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

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Q1. Scientific Question

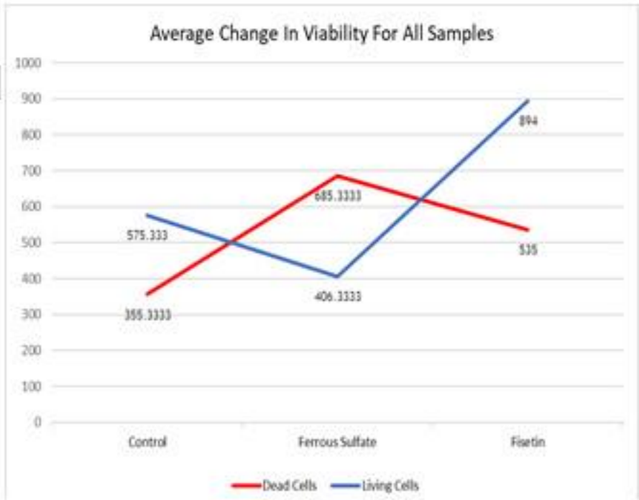
- How can doxorubicin-induced iron toxicity be inhibited?
- Will fisetin inhibit the Fenton Reaction and thereby inhibit hydrogen peroxide-mediated radical formation?
  - Fenton Reaction: $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^{\bullet} + OH^-$
- Can fisetin inhibit the progression of the cell death cycle?

Q2. Methodology

- Apply ferrous sulfate solutions to experimental cell groups, but not untreated controls
- Suspend samples in a 1% methylene blue solution (cell death indicator), and observe samples under a microscope on a hemocytometer grid
- Apply fisetin solution to the ferrous sulfate treated yeast, suspend samples in a 1% methylene blue solution
- Perform a cell death count (over 10,000 cells) and molecular dynamic docking simulation between fisetin and caspase 9

Q3. Data Analysis & Results

- Ferrous sulfate treatment resulted in the highest cell mortality rate (62.8%)
- Fisetin treatment lowered the cell mortality for the ferrous sulfate group (37.4%)
- Fisetin exhibits a 8.86 µM inhibition constant when binded to caspase 9



Change in viability across the three experimental groups- *student generated*

Q4. Interpretation & Conclusions

- Fisetin is able to reverse the effects of iron overload by inhibiting the progression of the cell death pathway
- Fisetin binds into the exosite of caspase 9 and thereby can alter the caspase 9 active site
- Fisetin is a candidate molecule to inhibit hydrogen peroxide-mediated radical formation and thereby the Fenton Reaction

Fisetin (red) binded to exosite F, H224 position of caspase 9 (blue)- *student generated*