Year II: Assessing Marine Bivalves as Novel Invertebrate Models for Targeting Anti-apoptotic BCL-2 Family Proteins in Blood Cancer: The in vivo Effects of Ursolic Acid and Gossypol Acetic Acid on Tumor Cells in Mercenaria mercenaria

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Anti-apoptotic B-cell leukemia/lymphoma (Bcl-2) family proteins are reported to be overexpressed in around half of all human cancers, linked to tumorigenesis, chemotherapy resistance, and poor prognosis. Effectively modeling this complex molecular interaction in leukemia is essential for its progression as a therapeutic target, yet the costliness and time-intensive nature of current models limit study. Disseminated neoplasia (DN), a transmissible cancer naturally occurring in the hemocyte "blood" cells of bivalve molluscs, shares notable molecular similarities to human leukemia. To determine functional similarities between human and bivalve Bcl-2, M. mercenaria was exposed to broad-spectrum Bcl-2 inhibitor AT101 at concentrations of 0.1 mg/kg, 0.3 mg/kg, and 0.6 mg/kg. Significant cytotoxicity caused to both tumor and normal cells in the treatment group above the dose threshold suggests DN's dose-response concordance with human sensitivity, and changes in cell viability, tumor cell fraction, and lipid accumulation paralleled responses in human studies at 0.3 mg/kg. The combined effects of ursolic acid, a substance predicted with high binding affinity to Bcl-2 proteins, and bioenhancer piperine was also studied as a novel chemotherapeutic combination, yielding significantly slowed tumor growth ($p<0.02$), decreased lipid droplet production ($p<0.02$) and minimal cytotoxicity to normal cells. Results suggest the further exploration of ursolic acid and piperine as a selective therapeutic combination and highlight the capabilities of bivalves as effective in vivo cancer models, with potential applications in high-throughput drug screening, minimizing vertebrate testing, and reducing cost per specimen over 50-fold for early phases of novel drug candidate screening.

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