ABSTRACT

Assessment of Chemopreventive and Anti-Cancer Value of *Artocarpus Heterophyllus* Lam. in Colorectal Cancer

Isaac Jay Morrison

Colorectal cancer (CRC) ranks third for cancer mortality among those below the age of 50, necessitating improved treatment and prevention initiatives. A crude methanol extract from the wood of *Artocarpus heterophyllus* was found to be the most bioactive during a cytotoxicity screening of eighteen extracts from three plants. Following semi-purification, the bioactive phytochemical artocarpin was detected (via HPLC–MS–DAD) in fractions found to be highly cytotoxic against the human colorectal cancer cell line HT29. Following preparation of an 84% (*w*/w) artocarpin enriched extract, time-and concentration-dependent cytotoxicity was demonstrated against human colorectal cancerous HCT116 cells (IC_{50} value: 4.23µg/mL in 72h). The use of the AOM/DSS colitis-induced model in C57BL/6 mice, then revealed that the enriched extract suppressed tumor multiplicity, reduced the protein expression of proliferating cell nuclear antigen, and attenuated the gene expression of proinflammatory cytokines (*Il*-6 and *Ifn-γ*) and protumorigenic markers (*Pcna*, *Axin2*, *Vegf*, and *Myc) in vivo*. The extract also significantly ($p = 0.03$) attenuated (threefold) the gene expression of murine cytochrome P450 (*Cyp) 2c37*, a homolog to the human CYP2C9 enzyme. Furthermore, given the role and overexpression of CYP1 and CYP2C families in various models of human cancer, the impact of artocarpin was evaluated on the activity of these enzymes. The enriched extract was shown to be a potent, irreversible inhibitor of CYP2C9 activity (IC_{50} value: 0.46 µg/mL) while pure artocarpin was a potent irreversible, time-dependent inhibitor of CYP1A1 activity (KI: 0.62±0.54µM; Kinact: 0.04±0.02min^{-1}) with binding likely at an allosteric binding site of CYP1A1 (binding affinity: −29.7$kJmol^{-1}$). *In vitro* CYP1A inhibition was then validated using 24hpf zebrafish (*Danio rerio*) embryos for PCB-126-induced and non-induced Cyp1a activity for the extract (0.09-3.4µg/ml). These promising chemopreventive, cytotoxic, anti-cancer and anti-inflammatory responses validate further evaluation of the enriched artocarpin *A. heterophyllus* extract as a potential therapeutic agent in the treatment of colorectal cancer.

Keywords: Artocarpin; Anti-cancer; Chemopreventive; Anti-inflammatory; Cytotoxicity; *Artocarpus heterophyllus;* jackfruit; zebrafish; mice; *in vivo*; *in vitro;* Cytochrome P450; CYP; cancer cell line; colorectal cancer; HCT116; HT29; CYP2C; CYP1A.