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Anti-cancer Activity of Curcumin Analogs (PGV-1, CCA-1.1, and FCCB-1) Against Irregular p53 Cancer Cell Lines and In Vivo Study
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ABSTRACT

Targeting p53 activity has been suggested as an important strategy in cancer therapy, including curcumin and its analog. Among those analogs, PGV-1, CCA-1.1, and FCCB-1 are potential for cancer therapy development. CCA-1.1 and FCCB-1 show improvement, compared to that of PGV-1, in their solubility, stability, and chemical properties that are vital in the scaling-up formulation. This study evaluated and compared the chemotherapeutic potency of CCA-1.1, *in vitro* and *in vivo*. FCCB-1 was also investigated further by cytotoxicity screening to be developed as an anti-cancer or boron neutron capture therapy (BNCT) agent.

WiDr and T47D cell lines with p53-mutant were used as *in vitro* models for colon and estrogen receptor (ER)-positive breast cancer cell, respectively, while 4T1 served as triple-negative breast cancer (TNBC) with p53 deficiency. MTT and trypan blue exclusion assays were used for the cytotoxicity assay. Cell cycle analysis was performed using flow cytometry with propidium iodide (PI) staining, followed by apoptosis test with Annexin V-PI staining, and intracellular ROS test with DCFDA-staining. The senescence incidence was observed with X-gal staining while the mitotic cells were assessed by May-Grunwald-Giemsa staining. Migration assay was performed by the scratch wound healing assay and the activity of MMP9 was observed by the gelatin zymography. For *in vivo* study, DMH-induced rat was used as a colon cancer model. Additionally, bioinformatic studies were incorporated to predict the compounds' targets.

PGV-1 and CCA-1.1 exhibited potent cytotoxic activity in WiDr (with IC_{50} of 10 and 5.4 μM, respectively) and T47D (with IC_{50} of 7 and 8 μM, respectively) cells, with less toxicity in non-cancerous cells. CCA-1.1 mimicked PGV-1 in targeting cell cycle arrest of WiDr cells at the G2/M phase, which simultaneously induced apoptosis, increased ROS level, caused cell senescence, and inhibited cell migration. In T47D cells, CCA-1.1 and doxorubicin showed a synergistic effect. Oral administration of CCA-1.1 inhibit tumor growth *in vivo* better than PGV-1. On the other hand, FCCB-1 showed its potency as a chemotherapeutic agent in 4T1 TNBC cells. The ADME prediction from pkCSM showed that FCCB-1 exhibited low log P and high solubility in water. FCCB-1 increased G2/M phase accumulation, with specific mitotic catastrophe generation in 4T1 cells. In addition, through bioinformatic analysis, FCCB-1 target proteins mainly play a role in cell cycle progression. Overall, the molecular mechanism of PGV-1, CCA-1.1, and FCCB-1 is possibly trough cell cycle arrest, enhancing ROS production, apoptosis and cellular senescence induction, and cell migration inhibition. Therefore, these compounds are prominent to be developed further as chemotherapeutic candidate drugs for colon and breast cancer therapy, particularly for irregular status of p53 cancer type.

Keywords: PGV-1, CCA-1.1, FCCB-1, irregular p53, colon cancer; breast cancer; cell cycle arrest, carcinogenesis