Salicin as a Multipurpose Therapeutic Approach for Colon Cancer

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ABSTRACT

There is a growing mass of literature pointing at COX2 inhibition as a promising option against CRC. Because of this, our study investigated the potential of the natural COX inhibitor salicin as a multipurpose drug void of complications found with the use of conventional COX2 inhibitors. Salicin's therapeutic potential was modeled at three time points in CRC development: before carcinogenesis, during carcinogenic changes, and after cells turned cancerous. Cellular results demonstrated salicin's ability to selectively kill and hamper the growth of human CRC cells while protecting healthy cells from carcinogenesis. Molecular results suggest that salicin normalizes oncogenic gene expressions. Specifically, salicin selectively promoted apoptosis and cell cycle arrest in CRC cells while interfering with metastatic, pain, and inflammatory pathways. Most importantly, our study suggests salicin avoids both gastrointestinal and cardiovascular complications by balancing its significant inhibition of COX2 with a slight inhibition of COX1. Overall, our study proposes salicin as a safe, multipurpose therapeutic drug that may potentially improve current CRC treatment options and patient outcomes.

I. INTRODUCTION

Tumor viability, inflammation, carcinogenesis, pain, metastasis, and angiogenesis all represent essential targets required for effective colon cancer treatment [1-3]. Growing evidence points to Cyclooxygenase-2 (COX-2) inhibition as a multi-therapeutic option in colon cancer [4,5]. However, the efficacies of current COX-2 inhibitors are limited due to cardiovascular and intestinal toxicity [6,7]. Therefore, our study investigated the potential of the natural COX inhibitor salicin, which has been shown to have minimal intestinal and thrombotic toxicity [8], as a multipurpose drug void of complications found with the use of conventional COX-2 inhibitors.

II. METHODOLOGY

Salicin's effects on cancer viability, inflammation, carcinogenesis, pain, and metastasis were evaluated on the cellular, genetic, and transcriptional levels using the COLO320DM human colorectal adenocarcinoma cell line and CCD 841 CoN human normal colon epithelial cell line. Data were collected using Trypan Blue Staining coupled Hemacytometry and Image Analysis, conventional RT-PCR, and ELISA. Colon carcinogen, AOM, was treated on CCD 841 CoN cells to analyze salicin's pre- and post-treatment effectiveness in response to carcinogenesis. Statistical analysis was performed via one-way ANOVA followed by Post-Hoc Scheffe with significance defined as $p \leq 0.05$.

III. RESULTS

Significant dysregulation of the expression of cell cycling (CDK4 & CDK 6), apoptotic (BCL-2), metastatic (EGFR), and inflammatory (CXCL1 & IL6) genes were observed in COLO cells and CCD cells treated with AOM. Likewise, increased cell survival linked to increased proliferation was observed for these cells. Treatment with salicin 1μM decreased colon cancer cell proliferation rates from 144% to 113% at 24 hours and 187% to 130% at 48 hours, with 10μM decreasing proliferation rates to 108% at 24 hours and 119% at 48 hours. Additionally, salicin 1 and 10 μM induced 167% and 346% increase in colon cancer cell death at 4 hours; 250% and 3 96% increase in 24 hours; 280% and 549% increase in 48 hours. However, on CCD normal cells, salicin induced no significant change in cell death or proliferation rates. On the genetic level, salicin normalized oncogenic gene expressions via significant downregulation of BCL-2, EGFR, CXCL1, IL6, CDK4, and CDK6. Pre and post treatment of salicin 10μM 1 hour before or after AOM reduced the rate of carcinogenesis, indicated by normalized rates of cell death and proliferation. Lastly, significant downregulation of PGE2, the enzymatic product of COX2, to 76% in lysate and 70% in supernatant was observed with salicin 10μM treatment in COLO cells when compared to the COLO control. This was accompanied with a minimal COX1 inhibition to 91% of the CCD control on the genetic level.

IV. CONCLUSION

Overall, our results suggest that salicin may potentially serve as an effective multipurpose drug that can attenuate many of the cancer hallmarks. Our study, for the first time, demonstrated salicin's ability to selectively kill cancer cells, reduce carcinogenesis, inflammation, and analgesic pathways simultaneously. The minimal COX1 inhibition, along with previous studies suggesting minimal toxcitiy at micromolar concentrations, may explain how salicin has minimal intestinal and thrombotic side effects. Thus, salicin could potentially be incorporated into current therapies or be used as an adjuvant with few side effects to optimize colon cancer treatment.

KEYWORDS

Cyclooxygenase (COX); Cyclin Dependent Kinases (CDK), B-cell Lymphoma-2 (BCL-2); Epidermal Growth Factor Receptor (EGFR); C-X-C motif Ligand 1 (CXCL1), Interleukin 6 (IL6), Azoxymethane (AOM); Reverse Transcription Polymerase Chain Reaction (RT-PCR); Enzyme linked Immunosorbent Assay (ELISA)

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