Molecular Mechanisms of Taiwanin C to Inhibit Proliferation of T28 Oral Cancer Cells

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Oral cancer is the major life-threatening oral diseases. Chewing Areca nut (AN) is a popular oral habit in Taiwan and Asia, arecoline is a potent carcinogen in Areca nut (AN). Chronic exposure to Arecoline carcinogens in the upper aerodigestive tract causes genetic changes in the epithelial cells of the oral mucosa. Arecoline may induce proliferative activity, through activation of the EGFR receptor and its downstream mechanisms, promote the downstream protein COX2 over expression. We firstly generated an OSCC model in C57BL/6J Narl mice by 0.5mg/mL arecoline and 0.2mg/mL 4NQO carcinogen in drinking water for 8 weeks and 28 weeks to mimic the etiology of oral cancer patient in Asia. Mice were sacrificed and cell were cultured as T8 and T28 cancer cells.T8 and T28 cells showed double growth rate than the N28 normal cell, displayed higher endogenous EGFR,COX2 and β-catenin protein levels and more β-catenin and p-Tyr^{1068}EGFR nuclear accumulation, and T28 cell exhibited more significant change than T8 cells. However, the treatment of nature herbal product from Taiwania cryptomerioides Hayata, Taiwanin C significantly inhibited the cell viability and growth rate of T28 cells in a dose dependent manner. Taiwanin C also active P27 cell cycle negatory protein and reduce the cyclin A and cyclin E. Furthermore, we observed that Taiwanin C inhibit phosphorylated EGFR and Taiwanin C also reduce β-catenin translocate into nuclear, down-regulated its downstream protein cyclin D, Tbx3 and c-Myc. Besides, we found that Taiwanin C suppressed the p-ser^{9} GSK-3-β protein level to inactivate Wnt signaling,which resulted in the proliferative suppression of T28 primary oral squamous cancer cells.