Helioxanthin suppresses the EGFR/MAPK pathway to induce cell cycle arrest and inhibit T28 oral cancer cell proliferation.

Abstract

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, Helioxanthin significantly inhibited the cell viability and growth rate of T28 cells in a dose dependent manner. Hlioxanthin also active P27 cell cycle negatory protein and induce G2/M cell cycle arrest. Furthermore, we observed that Helioxanthin inhibit COX2, phosphorylated EGFR and ERK protein level and reduce the nuclear accumulation of p-Tyr^{1068} EGFR and activator protein-1(AP-1) family protein, c-fos. Taken together,

our data indicated that Helioxanthin down-regulated the EGFR/ERK/c-fos signaling pathway to inhibit COX2 expression and activated P27 to induce G2/M cell cycle arrest, which resulted in the proliferative suppression of T28 primary oral squamous cancer cells.


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