1′-Acetoxychavicol acetate inhibits growth of human oral carcinoma xenograft in mice and potentiates cisplatin effect via proinflammatory microenvironment alterations

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Abstract

Background: Oral cancers although preventable, possess a low five-year survival rate which has remained unchanged over the past three decades. In an attempt to find a more safe, affordable and effective treatment option, we describe here the use of 1′S-1′-acetoxychavicol acetate (ACA), a component of Malaysian ginger traditionally used for various medicinal purposes.

Methods: Whether ACA can inhibit the growth of oral squamous cell carcinoma (SCC) cells alone or in combination with cisplatin (CDDP), was explored both in vitro using MTT assays and in vivo using Nu/Nu mice. Occurrence of apoptosis was assessed using PARP and DNA fragmentation assays, while the mode of action were elucidated through global expression profiling followed by Western blotting and IHC assays.

Results: We found that ACA alone inhibited the growth of oral SCC cells, induced apoptosis and suppressed its migration rate, while minimally affecting HMEC normal cells. ACA further enhanced the cytotoxic effects of CDDP in a synergistic manner as suggested by combination index studies. We also found that ACA inhibited the constitutive activation of NF-κB through suppression of Iκκ/β activation. Human oral tumor xenografts studies in mice revealed that ACA alone was as effective as CDDP in reducing tumor volume, and further potentiated CDDP effects when used in combination with minimal body weight loss. The effects of ACA also correlated with a down-regulation of NF-κB regulated gene (FasL and Bim), including proinflammatory (NF-κB and COX-2) and proliferative (cyclin D1) biomarkers in tumor tissue.

Conclusion: Overall, our results suggest that ACA inhibits the growth of oral SCC and further potentiates the effect of standard CDDP treatment by modulation of proinflammatory microenvironment. The current preclinical data could form the basis for further clinical trials to improve the current standards for oral cancer care using this active component from the Malaysian ginger.

Keywords: 1′-Acetoxychavicol acetate, Alpinia conchigera, NF-κB, CDDP, Oral Cancer, HSC-4