A novel derivative of quinazolinone, HoLu-12 induces G2/M arrest and apoptosis in human oral squamous cell carcinoma cells

Kuo-Chu Lai¹, Yi-Ting Chia², Mann-Jen Hour³

¹Department of pharmacology, Tzu Chi University, Hualien, Taiwan, ²Institute of Pharmacology and Toxicology, Department of Medicine, School of Medicine, Tzu Chi University, Hualien, Taiwan, ³School of Pharmacy, China Medical University, Taichung, Taiwan

Oral squamous cell carcinoma (OSCC) is one of the common malignant diseases in the world. Through advances in multimodality therapies for the treatment of OSCC; however, the overall 5-year survival rate for OSCC patients remains at 50% without significant improvement over the past three decades. Therefore, it is necessary to develop novel potential therapeutic agents against human OSCC. Quinazolinone is a heterocyclic chemical compound having a unique place in the field of medicinal chemistry. Many quinazolinone derivatives possess a wide range of bioactivities such as antimicrobial, anti-inflammatory, anticonvulsant, analgesic, anthelmintic and anticancer activities. In this study, we examined the therapeutic potential of 16 synthetic quinazolinone derivatives in OSCC by the sulforhodamine B (SRB) cytotoxicity assay. Among them, HoLu-12 exhibited no cytotoxicity toward the human normal oral mucosa fibroblast (OMF) cells. However, HoLu-12 significantly reduced the viability of human OSCC cell lines (CAL27 and OECM-1). Cell cycle analysis revealed that HoLu-12 induced G2/M arrest in OSCC cells. Western blot analysis showed that treatment with HoLu-12 increased the expression of cleaved-Caspase3 and cleaved PARP in a dose-dependent manner. Subcutaneous xenograft model was performed to demonstrate that HoLu-12 could significantly inhibit OSCC growth in vivo with negligible body weight loss. In addition, we observed that combined treatment with HoLu-12 and 5-fluorouracil had a synergistic cytotoxic effect in OSCC cells. Taken together, these results suggest that HoLu-12 may have the therapeutic potential against human OSCC cells.