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EVALUATION OF CYTOTOXIC ACTIVITY OF CUCURBITACINS AND THEIR SEMISYNTHETIC DERIVATIVES

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ABSTRACT

Cucurbitacins (CUCs) are a group of tetracyclic triterpenoid compounds found mainly in species of the Cucurbitaceae family, known for their bitterness and toxicity. In the past years, many reports confirmed the cytotoxic and antitumor activities of some cucurbitacins. In the present work a cytotoxic screening with 51 cucurbitacins and their semisynthetic derivatives was performed by MTT colorimetric assay, and then, the mechanism of cell death was investigated for the most active ones, with an emphasis on CUC 18 and CUC 37. The CUC 18, a novel natural cucurbitacin, induced apoptosis on A549 cells, arrested the cell cycle at G2/M phase and led to a disruption of the actin cytoskeleton. These effects were attributed to inhibition of STAT3 and AKT signaling pathways, which led to down regulation of antiapoptotic genes transcription. The CUC 37, a novel semisynthetic derivative of cucurbitacin B, also induced apoptosis, cell cycle arrest at G2/M phase, and actin cytoskeleton disruption, however with concentrations about 30 times lower than the CUC 18. The CUC 37 targeted directly the EGF receptors, leading to a down regulation of the downstream signaling pathways of this receptor (ERK, PI3K/AKT, and STAT3) and, consequently, their antiapoptotic target genes. Besides, the CUC 37 showed more selectivity towards NIH3T3/v-RAF and NIH3T3/k-RAS cells, when compared to non-transformed cells (NIH3T3 wild type cells). Finally, the antitumor effect of CUC 37 was confirmed in an *in vivo* lung tumor model, employing transgenic mice (c-RAF-1-BxB). Taken together, these findings strongly suggest that CUC 37 is a promising drug candidate for the treatment of lung cancer.

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