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The Cancer Control Challenge:
Better Understanding It to Better Face It

IN SILICO EVALUATION OF CUCURBITACIN B: ANTITUMOR ACTIVITY PREDICTION AND IDENTIFICATION OF MOLECULAR TARGETS IN CANCER CELL LINES

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Introduction: Cucurbitacin B is a triterpenoid compound with well-documented antitumor potential, yet its molecular mechanisms remain insufficiently explored across various cancer types. **Objectives:** This *in silico* study aimed to evaluate the antineoplastic potential of cucurbitacin B by predicting its biological activity and its effects on gene expression profiles in human cancer cell lines. **Methods:** An *in silico* study was conducted to evaluate the antineoplastic potential and molecular targets of cucurbitacin B. First, the compound's biological activity spectrum was predicted using PASS Online (Prediction of Activity Spectra for Substances), which analyzes structure–activity relationships based on the SMILES format. The platform provides probability scores for each predicted activity: Pa (probability of activity) and Pi (probability of inactivity). Only activities with Pa > 0.7 were considered biologically relevant, with emphasis on antineoplastic, cytotoxic, pro-apoptotic, and chemopreventive potentials. Subsequently, the DIGEP-Pred tool (Drug-Induced Gene Expression Profile Prediction), available through the Comparative Toxicogenomics Database (CTDbase), was used to predict gene expression changes induced by cucurbitacin B. The analysis focused on the VCaP prostate cancer cell line model (24-hour exposure). The tool predicts upregulated and downregulated genes based on the chemical structure, allowing the identification of key molecular targets affected by the compound. The list of downregulated genes was further analyzed to identify biological processes and pathways potentially impacted by cucurbitacin B. Special attention was given to genes involved in DNA repair, cell cycle progression, protein synthesis, and apoptosis—mechanisms commonly dysregulated in cancer. **Results:** High predictive activity values (Pa) were observed for general antineoplastic potential (Pa=0.968), lung cancer (Pa=0.883), sarcoma (Pa=0.866), cervical cancer (Pa=0.814), apoptosis induction (Pa=0.948), cytotoxicity (Pa=0.788), and chemoprevention (Pa=0.716). In the glioblastoma cell line SF-268, the compound showed a predictive activity of Pa=0.716. Notably, in prostate cancer cells, 24 genes exhibited Pa>0.9, suggesting strong sensitivity to cucurbitacin B. Transcriptomic profiling using the VCAP_24h model revealed significant downregulation of genes associated with cell

proliferation, protein synthesis, DNA repair, and cell cycle regulation, including *C12ORF48, EIF2B1, ATR, AURKA, ERCC2, RPL7A, RPS29, RPS12*, and *CCNF*. The modulation of these targets suggests that cucurbitacin B interferes with multiple essential cellular pathways, particularly in prostate cancer. **Conclusion:** These findings indicate that cucurbitacin B has a promising antineoplastic profile with multitarget activity across diverse cancer types. Its ability to modulate key oncogenic pathways supports its potential application in the development of targeted and personalized cancer therapies, especially those based on natural compounds.

Keywords: cucurbitacin B; cancer; antineoplastic.