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# Combined effects of paclitaxel and dichloroacetate on oral cancer metabolism

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## Abstract

**Background:** Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity [1]. Despite therapeutic advances, including the use of paclitaxel (PTX), treatment efficacy remains limited due to drug resistance and toxicity. The Warburg effect, characterized by enhanced aerobic glycolysis and acidification of the tumor microenvironment, contributes to resistance to anticancer therapies [2,3]. Dichloroacetate (DCA), a modulator of mitochondrial metabolism, represents a promising strategy to restore oxidative phosphorylation and promote apoptosis in cancer cells [4,5]. **Objective:** This study aimed to evaluate the effects of DCA, alone or in combination with PTX, on tumor metabolism and cell viability in OSCC cell lines (SCC25 and SCC09), compared to non-tumor oral keratinocytes (HOK). **Methods:** The cytotoxicity of DCA and PTX was evaluated using the sulforhodamine B (SRB) assay to determine the $GI_{50}$ values in SCC09, SCC25, and HOK cells. The Combenefit platform was used to analyze DCA/PTX combinations and identify synergistic interactions in SCC25 cells. **Results:** Both DCA and PTX reduced the viability of OSCC cells after 24 hours. PTX exhibited higher cytotoxicity than DCA, affecting both tumor and normal cells, indicating limited tumor selectivity. In contrast, DCA displayed moderate cytotoxicity with variable sensitivity among cancer cell lines and no detectable $GI_{50}$ in HOK cells under the tested conditions. **Conclusions:** PTX showed potent cytotoxic effects but lacked selectivity for tumor cells, whereas DCA exhibited moderate cytotoxicity and minimal impact on normal cells. Notably, combination analysis revealed multiple synergistic interaction points between DCA and PTX in OSCC cells, supporting their complementary mechanisms of action. These findings suggest that DCA may enhance the therapeutic efficacy of PTX while potentially allowing dose reduction and improved tumor selectivity.

**Keywords:** oral cancer; dichloroacetate; paclitaxel; tumor metabolism

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