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Impact of lipid nanoencapsulation on the cytotoxic profile of cannabidiol in melanoma cells

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ABSTRACT

Introduction: Despite major advances in melanoma therapy, including immune checkpoint inhibitors and targeted treatments, resistance, recurrence, and adverse effects remain significant clinical challenges. Cannabidiol, a non-psychotropic cannabinoid derived from *Cannabis sativa*, has demonstrated potential anticancer activity in preclinical studies, but its effects in melanoma remain poorly explored. Additionally, poor aqueous solubility and variable bioavailability limit cannabidiol's therapeutic potential, highlighting the need for improved delivery strategies.
Objectives: To evaluate and compare the *in vitro* cytotoxic effects of free cannabidiol and cannabidiol-loaded lipid nanoparticles in metastatic melanoma cells and to determine whether nanoparticle encapsulation enhances selectivity toward cancer cells relative to non-tumoral keratinocytes.
Methodology: Metastatic melanoma cell lines (A-375 and MeWo) and human keratinocytes were exposed to free cannabidiol or cannabidiol-loaded lipid nanoparticles (mean diameter of 206.9 ± 3.5 nm, polydispersity index < 0.25 and zeta potential of −27.9 ± 0.1 mV; characterization performed after 8 weeks of refrigerated storage) at equivalent cannabidiol concentrations ranging from 0.05 to 100 µM for 24 and 48 hours. Cell viability was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide reduction assay to evaluate concentration- and time-dependent cytotoxicity and compare the effects of free and encapsulated cannabidiol. Concentration–response curves were fitted by nonlinear regression using a log(inhibitor) versus normalized response model

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with variable slope, selected based on goodness-of-fit. IC_{50} values were compared using the extra sum-of-squares F test, with statistical significance set at $p < 0.05$.

Results: Free cannabidiol induced concentration-dependent cytotoxicity in all cell lines. Human keratinocytes cells were the most sensitive, with IC_{50} values at 24 hours of 4.6 μM, followed by A-375 (IC_{50} 5.1 μM) and MeWo (IC_{50} 5.8 μM) cells ($p = 0.006$). Similar values were observed at 48 hours ($p > 0.05$), indicating no significant time-dependent effect, except for MeWo cells (IC_{50} 4.6 μM, $p = 0.027$). Cannabidiol-loaded lipid nanoparticles demonstrated concentration- and time-dependent cytotoxicity in both melanoma cell lines, with significantly greater effects in MeWo cells compared with free cannabidiol at both 24 and 48 hours (IC_{50} 4.7 and 3.2 μM, respectively). Importantly, cannabidiol-loaded lipid nanoparticles exhibited markedly lower toxicity than free cannabidiol in human keratinocyte cells at both 24 hours (IC_{50} 8.3 vs 4.6 μM, $p < 0.0001$) and 48 hours (IC_{50} 8.6 vs 3.9 μM, $p < 0.0001$), suggesting improved selectivity toward tumor cells. Placebo nanoparticles (vehicle control) did not affect cell viability at the highest concentration tested.

Conclusion: Free cannabidiol showed similar cytotoxicity in human keratinocytes and melanoma cells, indicating limited selectivity. In contrast, lipid nanoparticle encapsulation enhanced the cytotoxic efficacy of cannabidiol in melanoma cells, particularly in the MeWo metastatic cell line, while reducing toxicity to normal keratinocytes. Cannabidiol-loaded lipid nanoparticle formulations may therefore represent a promising strategy to improve the therapeutic profile of cannabidiol in melanoma treatment, supporting the future development of nanotechnology-based drug delivery systems in oncology.