World Academy of Science, Engineering and Technology
International Journal of Pharmacological and Pharmaceutical Sciences
Vol:15, No:04, 2021

Integrating Non-Psychoactive Phytocannabinoids and Their Cyclodextrin Inclusion Complexes into the Treatment of Glioblastoma

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Abstract : Glioblastoma multiforme (GBM) remains a serious health challenge, as current therapeutic modalities continue to yield unsatisfactory results, with the average survival rarely exceeding 1-2 years. Natural compounds still provide some of the most promising approaches for discovering new drugs. The non-psychotropic cannabidiol (CBD) deriving from Cannabis sativa L. provides such promise. CBD is endowed with anticancer, antioxidant, and genoprotective properties as established in vitro and in in vivo experiments. CBD's selectivity towards cancer cells and its safe profile suggest its usage in cancer therapies. However, the bioavailability of oral CBD is low due to poor aqueous solubility, erratic gastrointestinal absorption, and significant first-pass metabolism, hampering its therapeutic potential and resulting in a variable pharmacokinetic profile. In this context, CBD can take great advantage of nanomedicine-based formulation strategies. Cyclodextrins (CDs) are cyclic oligosaccharides used in the pharmaceutical industry to incorporate apolar molecules inside their hydrophobic cavity, increasing their stability, water solubility, and bioavailability or decreasing their side effects. CBD-inclusion complexes with CDs could be a good strategy to improve its properties, like solubility and stability to harness its full therapeutic potential. The current research aims to study the potential cytotoxic effect of CBD and CBD-CDs complexes CBD-RMβCD (randomly methylated β-cyclodextrin) and CBD-HPβCD (hydroxypropyl-b-CD) on the A172 glioblastoma cell line. CBD is diluted in 10% DMSO, and CBD/CDs solutions are prepared by mixing solid CBD, solid CDs, and dH2O. For the biological assays, A172 cells are incubated at a range of concentrations of CBD, CBD-RMβCD and CBD-HPβCD, RMβCD, and HPβCD (0,03125-4 mg/ml) at 24, 48, and 72 hours. Analysis of cell viability after incubation with the compounds is performed with Alamar Blue viability assay. CBD's dilution to DMSO 10% was inadequate, as crystals are observed; thus cytotoxicity experiments are not assessed. CBD's solubility is enhanced in the presence of both CDs. CBD/CDs exert significant cytotoxicity in a dose and time-dependent manner ($p < 0.005$ for exposed cells to any concentration at 48, 72, and 96 hours versus cells not exposed); as their concentration and time of exposure increases, the reduction of resazurin to resofurin decreases, indicating a reduction in cell viability. The cytotoxic effect is more pronounced in cells exposed to CBD-HPβCD for all concentrations and time-points. RMβCD and HPβCD at the highest concentration of 4 mg/ml also exerted antitumor action per se since manifesting cell growth inhibition. The results of our study could afford the basis of research regarding the use of natural products and their inclusion complexes as anticancer agents and the shift to targeted therapy with higher efficacy and limited toxicity. Acknowledgments: The research is partly funded by IKY (State Scholarships Foundation) – Post-doc Scholarships-Partnership Agreement 2014-2020.

Keywords : cannabidiol, cyclodextrins, glioblastoma, hydroxypropyl-b-Cyclodextrin, randomly-methylated-β-cyclodextrin
Conference Title : ICPNDDS 2021 : International Conference on Pharmaceutics and Novel Drug Delivery Systems
Conference Location : London, United Kingdom
Conference Dates : April 22-23, 2021