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**“Unlocking Nature’s Secrets: Investigating Blueberry Extract as a Melanoma  
Therapeutic”**

Despite only accounting for 5% of skin cancers, melanoma displays a highly aggressive nature, as it constitutes over 75% of skin cancer-associated fatalities. In the pursuit of seeking effective treatments to either eliminate cancerous cells or reduce the disease progression, patients and their families often become financially burdened with healthcare expenses. Therapies that are accessible and cost-effective can significantly reduce medical debt, alleviating patients from the additional stress of healthcare costs on top of their life-changing diagnosis. Previous studies suggest that antioxidants play a role in impeding tumor growth and improving disease control in various cancer types. With all of this in consideration, the goal of this study is to assess the efficacy of blueberry extract as a promising yet affordable therapeutic candidate for melanoma. In this study, human melanoma A-375 cells were treated with increasing concentrations of blueberry extract and Doxorubicin to determine the inhibitory concentration,  $IC_{50}$ . The percentage viability of the treated cells was assessed using the MTS assay at 24 and 48h respectively. Representative brightfield images of the cells following the drug treatment were also captured. Based on the  $IC_{50}$  concentration, A375 cells were treated with either Doxorubicin or blueberry alone or in combination across a 2D-monoculture and 3D-cultures for 48h. Cellular growth was inhibited upon Doxorubicin and blueberry treatment in both the 2D- and 3D cultures of A375 cells. Consistently, the results obtained from IncuCyte Live-Cell Analysis System also confirmed the inhibition of A375 spheroidal growth upon the drug treatment. In agreement with the previous findings, Doxorubicin resulted in reduced cell growth. Interestingly, cells treated with blueberry extract alone displayed reduced growth highlighting the potential of blueberry extract to suppress A375 cell growth. To further investigate the effect of blueberry extract on regulating the EMT-like phenotype within the A375 cells, qPCR analysis of epithelial: E-cadherin, beta-catenin, and mesenchymal: N-cadherin and Vimentin markers was performed. The decreased cell viability coupled with regulation of these proposed markers upon drug treatment may provide a basis for future exploration. The observed regulation has the potential to facilitate accessible and cost-effective interventions in the fight against this aggressive skin cancer. Further, a 3D-multicellular organoid model comprising of A375 cells, human fibroblast (HF-1), and human umbilical endothelial cells (HUVEC) is being developed to validate the efficacy of this combination treatment.