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“The influence of fisetin-loaded liposomes on therapy-induced senescent cells”

Cellular senescence refers to a state of growth arrest in which cells remain metabolically active. Various stressors, including chemotherapeutic agents can trigger this condition. Senescent cancer cells may contribute to tumorigenesis through multiple pathways, including influencing the tumor microenvironment by secreting SASP (Senescent Associated Secretory Phenotype) or by escaping cell cycle arrest, which can ultimately lead to cancer relapse. Innovative strategies, such as advanced drug delivery systems based on nanoparticles, are being developed to improve the efficiency of therapeutic agents. Combining these drug delivery systems with senotherapy, an approach that selectively targets senescent cells, could offer a promising solution for reducing the risk of cancer recurrence.

This thesis is focused on examining the induction of cellular senescence and investigating cell viability, particularly in the context of cancer treatment. The research explored how drug delivery systems utilizing liposomes with encapsulated Fisetin can influence two senescent cell lines: A549 (lung carcinoma) and WI38 (lung fibroblast). The study describes protocols for inducing cellular senescence using doxorubicin, assessing cell viability following doxorubicin treatment, and evaluating various senescence markers. The research emphasizes the complexity of cellular responses to chemotherapeutic agents and underscores the need for comprehensive biomarker analysis to characterize senescent cells accurately. This study comprehensively examines liposomes' preparation, characterization, and evaluation as drug delivery systems for the water-insoluble senotherapeutic drug Fisetin. Utilizing established methodologies for liposome prepartion, particularly the thin-film hydration method, the study focuses on optimizing liposome size and encapsulation efficiency, which are critical factors for effective therapeutic applications. The study evaluated Fisetin's cytotoxicity on senescent versus non-senescent cells, revealing that it lacks selective apoptosis properties and affects both cell types at higher concentrations. While Fisetin did not demonstrate senolytic properties in the A549 and WI38 cell lines, it exhibited senomorphic effects by modulating the secretion of pro-inflammatory cytokines IL-6 and IL-8. Encapsulating Fisetin in liposomes enhanced its efficiency compared to the free form of this senotherapeutic drug. The findings suggest that although Fisetin does not effectively eliminate senescent cells, it may reduce their harmful effects through senomorphic actions.