

Abstract

The first chapter outlines the pathological features of glioblastoma (GBM), including genomic instability, BBB-associated drug resistance, and an immunosuppressive tumour microenvironment. It also highlights the role of adenosine deaminase 2 (ADA2) and tumour-associated macrophages (TAMs) in glioma progression, while introducing flavonoid-based therapeutic strategies targeting ADA2-mediated immunosuppression, reactive oxygen species (ROS) induced DNA damage, and blood brain barrier (BBB) targeted nano formulations for enhanced anti-glioma efficacy.

The second chapter focused on the screening of a selective ADA2 inhibitor from structurally diverse flavonoids, leading to the identification of daidzin (DZN) as a potent high-affinity ligand with marked selectivity for ADA2 over ADA1, another adenosine deaminase isoform essential for purine metabolism, as revealed through molecular docking studies. Molecular dynamics simulations and surface plasmon resonance analyses further established stable ADA2–DZN interactions with greater binding stability than the standard ADA2 inhibitor, coformycin. In glioma co-culture systems, DZN selectively inhibited ADA2 activity, promoted TAM repolarization from the immunosuppressive M2 phenotype toward the pro-inflammatory M1 phenotype.

The third chapter demonstrates that DZN interacts with the DNA helix via a noncanonical intercalative mode, leading to oxidative destabilization of the DNA structure, as revealed through molecular dynamics simulations. Additionally, frontier orbital hybridization analyses identified DZN as an electron-accepting intercalator, while transmission electron microscopy imaging confirmed extensive DNA fragmentation at concentrations lower than standard DNA intercalating agent, doxorubicin. Notably, DZN exhibited superior anti-glioma efficacy compared with the standard drug temozolomide, with minimal toxicity toward normal astroglia. It induced extensive DNA damage evidenced by γ -H2AX activation and 8-OHdG formation in GBM cells, and produced significant tumour suppression in C6 glioma xenografts without evident systemic toxicity.

The fourth chapter focuses on overcoming BBB-associated limitations in GBM through the development of a sphingomyelin based liposomal nanoplatform (DSPMC Lipos) for targeted DZN delivery in the brain. DSPMC Lipos exhibited uniform nanoscale vesicles (~80-100nm), rapid release kinetics, and enhanced anti-glioma efficacy, achieving ~80% tumour regression in C6 rat glioma model. Moreover, the nano formulation efficiently crossed the BBB and showed sustained brain accumulation following intravenous administration in sprague–dawley rats.

The final chapter concludes that daidzin acts as a multifunctional glioblastoma therapeutic through ADA2 inhibition, TAM reprogramming, ROS-mediated cytotoxicity, and DNA destabilization, while liposomal nanoengineering significantly enhances BBB penetration and therapeutic efficacy.

Keywords: Glioblastoma (GBM); Adenosine deaminase 2 (ADA2); Daidzin (DZN); Tumour-associated macrophages (TAMs); DNA Intercalation, Reactive oxygen species (ROS); Blood–brain barrier (BBB); Liposomal nano formulation.

