Abstract

The thesis entitled *"Development of Theranostic Systems for Neurodegenerative Disorder*s" presents the development of multifunctional theranostic systems aimed at the detection and treatment of neurodegenerative disorders, with a primary focus on $A\beta_{42}$ aggregation linked to traumatic brain injury. The research leverages mesoporous silica nanoparticles and chalcone derivatives to create innovative platforms capable of crossing the blood-brain barrier, targeting $A\beta_{42}$ plaques, and delivering therapeutic agents effectively.

Chapter 1: Introduction

This chapter provides a concise introduction to neurodegenerative disorder, emphasizing the significance of abnormal protein aggregates. The chapter explores challenges in treating these disorders, such as the blood-brain barrier, which restricts most diagnostic and therapeutic agents. The potential of mesoporous silica nanoparticles as theranostic nanocarriers is discussed, highlighting their high surface area, biocompatibility, and modifiable surface for drug delivery and imaging applications. Molecular imaging techniques, including SPECT and MRI, are introduced as critical diagnostic tools to visualize and monitor the disease.

Chapter 2: Chalcone Functionalized Mesoporous Silica Nanoparticles for Diagnosis and Therapy of Trauma-Induced Aβ Aggregation

The focus of the study lies in the design of functionalized mesoporous silica nanoparticles with the aim towards enhanced permeability across the blood-brain barrier while ensuring effective binding to $A\beta_{42}$ aggregates. Chalcone and diethylenetriamine pentaacetic acid functionalized mesoporous silica nanoparticles, were characterized via FESEM and TEM, which displayed spherical morphology and homogeneous size distribution. Results based on nitrogen adsorption/desorption isotherms, TGA, FTIR, and UV-Vis analysis confirmed functionalization on MSN with targeting moiety, chalcone, and chelating agent, DTPA. A red shift to 30 nm and 4-fold increase in emission intensity of flurorescent spectrum of nanomaterial upon treatment with $A\beta_{42}$ aggregate, indicated interaction between $A\beta_{42}$ aggregate and synthesized material. The MTT assay indicated > 90% cell viability in PC12 and HEK-293 cell lines after co-incubation with nanoparticles at 48 h. Radiolabelled complex of synthesized nanomaterials with SPECT radioisotope, ^{99m}Tc, had >99% radiochemical purity. *In vivo* SPECT imaging on healthy rabbits demonstrated the effective penetration of functionalized nanoparticles to the brain. Further, non-surgical rmTBI model over-expressed with $A\beta_{42}$ plaques was developed, and the formation of $A\beta_{42}$ plaques was confirmed using histological analysis, ThS staining, and immunohistochemistry. *Ex vivo* biodistribution studies revealed high brain uptake of functionalized nanoparticles in $A\beta_{42}$ plaques over expressed TBI mice after 2 h with slow washout, compared to control mice, possibly due to binding of nanoparticles with $A\beta_{42}$ aggregates. Further, curcumin was loaded in nanoparticles, exhibited biphasic sustained release profile, underscoring potential of the system for controlled drug delivery. These findings suggest that chalcone- and DTPA-functionalized mesoporous silica nanoparticles hold promise for theranostic applications in neurodegenerative disease management.

Chapter 3: Multi-Target Directed Triazole−Chalcone Conjugate as Potent Aβ42 Aggregation Inhibitor

This chapter discusses the design and synthesis of triazole-chalcone conjugate (L1) targeting Aβ42 aggregation. The conjugate exhibits high binding affinity and Aβ aggregation inhibition due to its dimeric structure, selected through molecular docking and molecular dynamics studies. The conjugate also chelates metals such as Cu^{2+}, showing potential in mitigating metal-induced oxidative stress. The findings indicate L1 as a promising multifunctional agent for addressing amyloid plaques and related neurodegenerative pathways.

Chapter 4: Binding Studies of Triazole−Chalcone Conjugate with Serum Albumin Proteins

This chapter explores the pharmacokinetics of the triazole-chalcone conjugate (L1) through its interaction with bovine serum albumin using spectroscopic and in silico techniques. Binding studies reveal moderate affinity, with static quenching suggesting non-covalent interaction. Molecular docking confirms hydrogen bonds and Van der Waals interactions as primary binding forces. These insights into the pharmacokinetics of L1 highlight its potential for clinical applications as a therapeutic agent.

Chapter 5: Folate Receptor Targeted Mesoporous Silica Nanoparticles as Dual Imaging Probe

This study describes the development of ^{99m}Tc-labeled manganese oxide-loaded mesoporous silica nanoparticles conjugated with folic acid as targeting moiety and H_2pentapa-en-NH_2 as chelating agent, intended for targeted SPECT-MRI dual imaging applications. The synthesized nanoprobe was designed to leverage both paramagnetic and radiolabeling properties, enhancing imaging contrast for T1-weighted MRI and SPECT modalities. The nanoparticles were evaluated for biocompatibility in HEK-293 and U87MG cell lines, supporting their safety profile. The system demonstrated high radiolabeling stability and included pH-responsive release mechanism for manganese ions to optimize relaxivity for MRI. *In vivo* SPECT imaging demonstrated rapid tracer accumulation in U87MG xenografts with and minimal uptake was observed in non-targeted organs. *In vivo* MRI studies indicated strong tumor contrast at 2 h post injection. Given its desirable contrast enhancement in T_1 MRI and SPECT imaging, along with low toxicity, the developed system shows potential as an effective multifunctional nanoprobe for dual imaging.

Chapter 6 Summary of Thesis

This chapter highlights the salient features of this work. By integrating molecular imaging, drug delivery, and multitarget-directed therapeutic strategies, this work contributes significantly to the development of advanced nanomedicine platforms with broad potential for clinical applications.