Preface

Cancer remains one of the leading causes of mortality worldwide, posing significant challenges to healthcare systems and researchers alike. Despite numerous advancements in cancer therapy, the effective delivery of therapeutic molecules to cancer cells remains a significant hurdle. Traditional chemotherapeutics often suffer from poor aqueous solubility and limited availability at the intended region. Recognizing these challenges, researchers are delving into developing tumor microenvironment (TME)--responsive nanomedicine as a promising strategy for breast cancer therapy. This approach leverages the unique characteristics of the TME, such as lower pH, reactive oxygen species (ROS), redox imbalance, hypoxia, and enzymatic activity, to achieve targeted and controlled drug release, thereby enhancing treatment efficacy while minimizing systemic toxicity.

Chapter 1 provides an introduction to the biopolymer-based therapeutic approaches for targeted delivery of chemotherapeutics in breast cancer.

Chapter 2 comprehensively discusses various strategies employed in recent years to develop targeted therapeutic carriers that selectively deliver the drugs to cancerous cells.

Chapter 3 outlines the objectives and plan of work.

Chapter 4 focuses on preparing and characterizing HA-stabilized chitosan (CS) nanoparticles using the ionic gelation method. These nanoparticles were designed to entrap cabazitaxel (CBT), a potent chemotherapeutic agent, and were functionalized with Cetuximab (Cmab) to target epidermal growth factor receptors (EGFR) overexpressed on cancer cells. The nanoparticles were evaluated for various physicochemical characteristics, followed by *in vitro* and *in vivo* evaluation. *In vitro* studies demonstrated enhanced cytotoxicity, cellular uptake, and cellular responses, including mitochondrial depolarization and nuclear condensation, due to receptor-mediated endocytosis. The nanoparticles also showed improved pharmacokinetic performance and in vivo anti-tumor

efficacy, with minimal organ toxicity, highlighting their potential as effective drug carriers for targeted cancer therapy.

Chapter 5 covers the synthesis of chitosan oligosaccharide and vitamin E succinate conjugate, its evaluation, and its application in the development of a novel GSH-responsive Cetuximab-anchored chitosan/vitamin-E succinate conjugate-based hybrid nanoparticle. The chapter subsequently covers the characterization and evaluation of these spherical, sub-200 nm, cationic, and redox-responsive nanoparticles. *In vitro* evaluations showed significantly higher cytotoxicity against MDA-MB-231 cells, enhanced cellular uptake, and reduced mitochondrial membrane potential compared to free CBT. The *in vivo* pharmacokinetic studies indicated better performance of the nanoparticles, with improved half-life, area under the curve (AUC), and mean residence time (MRT). Further, the chapter discussed the tumor regression, survival, and histological data confirming these nanoparticles' efficacy and safety, demonstrating their potential as a targeted anticancer drug delivery platform.

Chapter 6 delves into the fabrication of targeted nanoparticles-loaded microneedles for localized drug delivery of cabazitaxel in DMBA-induced tumor-bearing SD rats. The article focuses on developing chitosan and hyaluronic acid-based amphiphilic conjugates with similar hydrophobic fragments. The fabrication of deformable HA-OA/CS-OA-based nanoparticles and loading of these particles in PVA/HA-based dissolving microneedles, followed by its *in vitro* and *in vivo* evaluation, forms the basic premise of this chapter.

Chapter 7 outlines the summary, conclusions, shortfalls, and future perspectives of all the objectives undertaken.

Chapter 8 lists all the references utilized to conduct this research.

Appendices provide a list of key publications from the work done during the doctoral research, and the first page of the publications from the work discussed in the thesis has been included.