ABSTRACT

Cancer is one of the leading causes of death throughout the world, in which the main treatments involve surgery, chemotherapy, and/or radiotherapy. An important characteristic of cancer cells is their uncontrolled proliferation, which does not respond to normal growth inhibition signals which in normal case limit the cell division. Hence there is urgency for developing new anticancer drugs targeting these signaling pathways. Another important aspect of these drugs is its acquired toxicities like nephropathy, retinopathy and cardio-toxicity. Antioxidant therapy plays an important in controlling these side-effects. The present thesis provides an account of novel drug designing strategies for anticancer compounds and also for new synthetic antioxidants useful in nephrotoxicity.

Chapter 1 provides literature review on general aspects on cancer and various cell signaling pathways during cancer growth. It also gives a brief account of different classes of compound currently used in cancer therapy. Additionally, this chapter highlights the current status of side-effects due to several drugs and importance of antioxidant enzymes in reducing the oxidative stress.

Chapter 2 of the thesis summarizes experimental strategies adopted in synthesis and characterization, molecular docking and anticancer activities of the novel compounds.

Chapter 3 deals with designing novel compounds for inhibition of COX-2/5-LOX enzymes against colon cancer cells. These compounds were found to be dual COX-LOX inhibitors active against panel of colon cancer cells at micromolar concentrations. Molecular docking studies revealed confirmation of their strong binding in the cavities of COX and LOX enzymes.

Chapter 4 highlights the drug design strategies for inhibition of anti-apoptotic bcl-2 family of proteins which operate through the apoptotic pathway. The compounds were active against variety of cell line including triple negative breast cancer (MDA-MB231) cells, Prostate cancer (PC-3) cells and pancreatic cancer (Bx-PC-3) cells. Molecular docking studies helped us to understand the binding of these molecules in the bcl-2 protein cavity.

Chapter 5 presents an account of the protective capability of synthetic Mn-SOD mimics against Xanthine-Oxidase induced kidney toxicities, commonly found in nephropathy in diabetic patients. The novel synthetic complexes were effective in increasing the viability of kidney cells during high ROS stressed conditions even at low concentration as low as 10nM.

Overall studies in the present thesis suggested the importance of developing novel drugs to target the signaling pathways for evolving potent anticancer compounds. In addition it suggests the role of synthetic antioxidant enzymes for ameliorating the oxidative stress generated due to these drugs. Thus the use of these antioxidants will help in protecting vital organs like kidney and heart from deleterious effects of oxidative stress.