Thesis title : **Mechanistic Insights into Bioactivity and Permeability of Natural Compounds for Selective Targeting of Cancer**

Submitted by : **Navaneethan Radhakrishnan (2017BEZ8438)**

Supervisor : **Prof. D. Sundar**

ABSTRACT

Cancer chemotherapy is often associated with serious adverse side effects. This is due to the lack of selectivity of drugs towards cancer cells. The need for selectivity led to the development of the targeted therapy approaches. Targeted therapy aims to selectively target cancer cells, however, drug resistance arising from heterogeneity of the tumor is an issue. To counter heterogeneity, molecules that could target multiple cancer pathways are considered promising. Several small molecules are actively being explored in cancer research for their therapeutic potential. Natural compounds are of great interest in cancer drug development due to their molecular rigidity and drug-like properties.

Cancer drug development is associated with high failure rates during clinical trials due to the lack of efficacy of the drug candidates. This could be overcome by proper elucidation of molecular mechanism of action of drug candidates during preclinical trials. Drug activity also depends on permeability of the active compounds through biological barriers like cell membranes. This study presents mechanistic insights into different modes of selectivity by focusing on bioactivity and permeability of few select natural compounds that are already reported for their anticancer properties.

In silico molecular modeling methods have been used to study the bioactivity and permeability of the chosen compounds. Molecular mechanisms underlying the anticancer activities of natural compounds fucoxanthin, withaferin A and caffeic acid phenethyl ester have been interpreted from protein-ligand docking and molecular dynamics simulation studies. The results suggested that fucoxanthin, withaferin A and caffeic acid phenethyl ester can cause p53 activation in cancer cells leading to apoptosis. Molecular dynamics simulations with umbrella sampling protocol were performed using lipid bilayer models to explore the effect of phosphatidylserine exposure in cancer cells on the membrane permeation of natural compounds withaferin A, withanone, caffeic acid phenethyl ester and artepillin C. The results indicated that the exposure of phosphatidylserines in cancer cell membranes facilitated the permeation of withaferin A, withanone, caffeic acid phenethyl ester through a cancer cell

membrane compared to a normal cell membrane. The presented data demonstrated the potential of drug-membrane interactions in rendering selectivity to drugs. An atomistic model of stratum corneum lipid matrix of skin for transdermal permeation studies of small molecules has been developed and validated with experimental data from literature. In summary, this thesis sheds light into specific molecular-level mechanisms underlying bioactivity and permeability using *in silico* modeling techniques that will aid in advancing the studied natural compounds as cancer drugs and develop new compounds for selective targeting of cancer.