# Abstract of the Thesis- SHIVANI GUPTA (166107106)

Alzheimer's Disease (AD) which is a progressive, neurodegenerative and geriatric disease is multi-faceted in nature with genetic, environmental and some unknown mechanism associated with it. The main culprit behind the etiology of the disease is believed to be the extraneuronal senile plaques made up of Amyloid-Beta (Aβ) proteins and intraneuronal neurofibrillary tangles (NFTs) of hyperphosphorylated tau protein. Amongst these two, Aβ fibrils have been reported to be the principal clinical hallmark due to its direct involvement in the neurotoxicity and degeneration leading to AD.

The therapeutic approaches have been broadly classified into two viz. inhibition of the aggregation of the Aβ monomers and disaggregation of the preformed Aβ fibrils. The use of β-sheet breakers, nanoparticles, small molecules and natural compounds have been studied for the same purpose. The failure of the clearance of the drugs from inhibition strategy has motivated the in depth investigations for the disaggregation approach. In this view the role of natural compounds have been preferred owing to their natural non-toxicity and biocompatibility with the human system.

In the present work, various natural compounds from different category have been studied by means of Molecular Dynamics (MD) simulation, wherein they were made to interact with disease relevant Aβ fibril (PDB ID: 2BEG). Herein the caffeine from alkaloids, caffeic acid, gallic acid, epigallocatechin and ellagic acid from polyphenols, omega-3 polyunsaturated fatty acids (PUFAs) and lycopene from terpene have been investigated. The mechanistic details on the interaction of caffeine (CFF) with preformed Aβ fibril has been obtained wherein the destabilization of the fibril is observed. Four major phenolics from plants have been screened by docking and studied by MD simulation for their destabilization potential. The outcome of the study observed ellagic acid (REF) as the best binder and destabilizer of Aβ fibril wherein

it binds to chain A of the fibril by accessing fibrillar cavity. The significant role of Omega -3 fatty acids, Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (HXA) specifically in destabilization of the Aβ fibril has been assessed. The crucial role of EPA and HXA in maintaining brain integrity and destabilization potential on Aβ fibril, makes them a suitable drug candidate for treating AD. The amphiphilic nature of these PUFAs was found to be the supportive for the better binding with the fibril, wherein polar head binds to K28 (positively charged residue) and long carbon tail to the hydrophobic residues of the fibril. This brings effective destabilization by compromising the inherent hydrophobic interactions coupled with loss of β sheet content. The detailed analysis of lycopene as a potential destabilizer of different polymorphic form of Aβ fibril has been done. The lycopene was found to interact with the surface and cavity of the fibril depending on the architecture. Conclusively, from all the studies, the major governing principles behind destabilization of the fibril was observed by loss of H-bonds, breakage of salt-bridges and loss of hydrophobic interactions in the fibril upon ligand introduction. The loss of β-sheet content indicates the collapse of highly organized structure indicating disorganization in the presence of the ligand curbing neurotoxicity of the fibril. The need to investigate the fate of the destabilized fibril upon removal of the ligand has also been conducted. This study highlights the enhancement of the destabilized structure upon removal of the ligand, REF in this case, thereby inhibiting the refibrillation, indicates towards the non-neurotoxicity of the fibril obtained. This establishes the efficacy and prophecy of destabilization of preformed Aβ fibril by natural compounds as a promising therapeutic approach for treating AD.