INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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Programme of Study	:	Ph.D.
Thesis Title:		Computer Simulation Studies of the Association of Caffeine Molecules in Aqueous Solution and its Role as an Inhibitor on Amyloid Aggregation
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Thesis Submitted to the Department/ Center	:	Chemistry
Date of completion of Thesis Viva-Voce Exam	:	25/1/2017
Key words for description of Thesis Work	:	Protein aggregation, Alzheimer's disease, caffeine, MD simulation

SHORT ABSTRACT

Over the past few years, several studies have proposed the link between caffeine intake and reduced risk of developing Alzheimer's disease, a neurodegenerative disease. However, the molecular mechanism of the therapeutic potential of caffeine is largely unknown. The entitled thesis seeks to address this issue by means of classical molecular dynamics (MD) simulation. We have carried out classical MD simulation to explore the underlying mechanism of effect of caffeine on aggregation of protein. We started our investigation to explore the self-association of caffeine molecules in presence of NaCl salt, as salt ions are an essential component of living systems. We observed that caffeine molecules self-aggregate by forming clusters by intermolecular π-stacking interaction. Addition of NaCl salt causes the exclusion of water molecules from caffeine hydrophobic surface. An investigation of the effect of temperature on self-association of caffeine molecules in pure water and salt solutions showed that as temperature increases, the probability of formation of higher order clusters decreases. Calculation of potential of mean force and the enthalpic and entropic contribution to it shows that thermodynamics of caffeine association is enthalpy driven in pure water. However, presence of salt leads to entropy driven association specifically at higher temperature. Our analyses point out the transition of thermodynamic behavior of caffeine association to shorter length-scale as the chemical and physical environments are changed. To shed lights on the effect of caffeine on hydrophobic aggregation of biomolecules, we have examined the self-aggregation of hydrophobic di-t-butyl-methane (DTBM) molecules in a regime of caffeine : DTBM stoichiometric ratios. We have observed the disruption of hydrophobic moieties of DTBM aggregates in 10 : 1 or more stoichiometric ratio of caffeine : DTBM. We have shown that caffeine aggregates form a hydrophobic environment around a DTBM molecule in which a DTBM molecule is encapsulated, and, these caffeine clusters physically block the other DTBM molecules to interact with the encapsulated DTBM molecule, leading to disruption of DTBM clusters in solutions with 10:1 or higher caffeine to DTBM molecules. Next, we have explored the effect of caffeine on protein aggregation, which is more complex compared to purely hydrophobic assocition. Our studies on effect of caffeine on the aggregation of amyloid-β derived switch-peptide with varied stoichiometric ratios of caffeine to peptide showed that formation of β-sheet conformation is prevented to a large extent in presence of

10:1 or more caffeine to peptide ratio. We have observed that caffeine can inhibit the formation of β-sheet by interacting with the peptide aromatic moiety. In order to understand the mechanism of inhibition action of caffeine in more detail, we have again considered the seven residue peptide $A\beta_{16-22}$, which form amyloid fibril in vitro. In pure water system, the peptides aggregate together to shield the hydrophobic central core from the solvent water molecules and the hydrophilic terminal residues are well exposed to water. In presence of caffeine the hydrophobic central core of peptides is blocked by the caffeine clusters to interact with other peptides. The interaction between caffeine and the phenylalanine residues of peptide restricts the self-assembly formation of peptide. We also observed that as the number of caffeine increases, the interaction of caffeine with the hydrophobic residues and hydrogen bonding sites of the peptide increases. With increasing caffeine number higher number of medium ordered caffeine clusters are formed. These clusters inhibit amyloid formation of peptide, by blocking of aromatic Phe residue of the peptide by peptide-caffeine π-stacking interaction, and other residues by hydrophobic and hydrogen bonding interactions leading to complete disaggregation of peptide in caffeine solution with 10:1 or higher caffeine to peptide stoichiometric ratio.