National Institute of Technology Rourkela

Defence Seminar

Seminar Title	: Conformations and Binding of Chondroitin Sulfate, Heparan Sulfate, and Hyaluronic Acid with CXCL8 in Aqueous Medium from Molecular Dynamics Simulation
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Venue	: Seminar Room, Chemistry Dept (For online : meet.google.com/tdg-ktrp-dow)
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Abstract	: Chondroitin sulfate (CS), Heparan sulfate (HS), and Hyaluronic acid (HA) are an important class of polysaccharides, widely known as glycosaminoglycans (GAGs). CXCL8 belongs to the chemokine family, one of their target proteins. The bound form of these molecules participates in various biological processes where sulfation patterns, charge density, and solvent reorganization around them bring massive heterogeneity and distinct topologies in the GAG conformations. The prime objective of this thesis is to explore the effects of sulfation on the conformations and binding of CS/HS/HA with CXCL8, the role of solvent, and understand the molecular mechanisms of the recognition process from the molecular dynamics (MD) simulation approach. The thesis comprises seven chapters. Chapter 1 includes a concise overview discussing the present state of knowledge, recent advancements in the field, and the methodologies employed in this thesis. Chapter 2 investigated the conformational properties of the disaccharide building units of CS, HS, and HA with varying degrees of sulfation position (except HA) in an aqueous medium at ambient temperature. The study revealed that although the flexibility of the disaccharide building blocks of the three GAGs is relatively different from each other, the increase in the degree of sulfation by one unit has limited effects on some of the properties of the molecules. Therefore, considering the GAG chain length in general, an in-depth study of the increased chain length of these molecules is necessary. As a result, in Chapter 3, the conformations of hexameric HA, CS(disulfated), and HS(di-sulfated) were studied in free forms and when bound with CXCL8 monomer thoroughly in aqueous medium at ambient temperature. The relative binding free energy of the complexes was computed to understand the feasibility of the process. Further, the kinetics of hydrogen bonds (HBs) involving conserved water in mediating the interactions between CXCL8 and CS/HS/HA were explored by adopting the Luzar-Chandler model. After notifying the heterogeneous effects of sulfation on the hexameric molecules, the impact of the degree of sulfation at more diverse positions on octadecasaccharide CS and HS molecules was carried out in Chapter 4 and Chapter 5, respectively. The binding of these molecules with CXCL8 dimer was explored, and the binding motif of the protein was identified. In these chapters, emphasis was given to identifying the preferred conformations and stability of different CS and HS molecules by adopting a k-means algorithm, constructing various free energy landscapes, and computing conformational entropy from dihedral flexibility. In Chapter 6 of the thesis, an attempt was made to understand the comparative binding phenomenon of the hexameric CS (di-sulfated) and HS (di-sulfated) molecules to CXCL8 monomer and dimer. The HB property and solvent contribution were investigated thoroughly to unfold the differential recognition phenomenon of these GAGs towards the CXCL8 monomer and dimer. The last chapter, Chapter 7 of the thesis, summarizes the important findings of all chapters as conclusions.