Computational Search for Druggable Sites: Solvation and Structural Studies on 3ZR9 New Delhi Metallo-ß-lactamase, NDM-1

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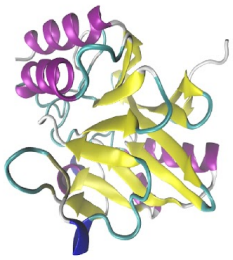
Abstract

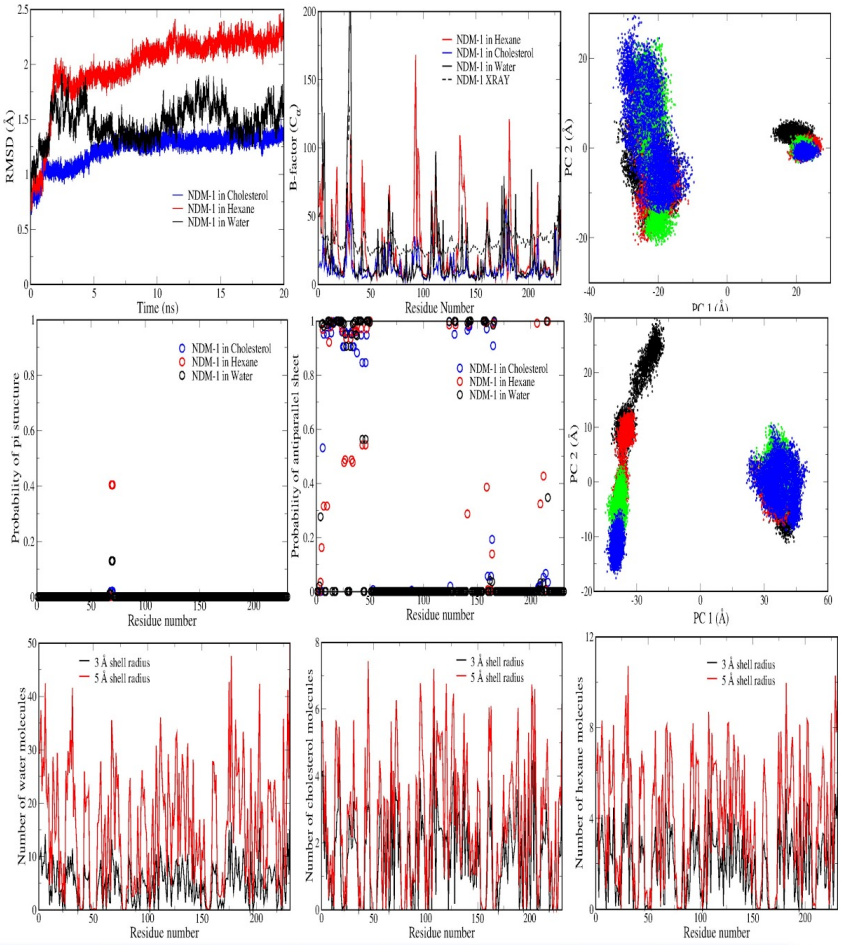
The rapid spread of antibiotic-resistant bacteria, ARBs, has paved the way to the emergence of new drug discoveries. One of which is New Delhi Metallo-beta-lactamase, NDM-1. This has alarmed different nations due to its capability of reducing or totally removing the antibiotic property of drugs and chemicals. Using the crystalline structure of NDM-1, a series of MD simulations were conducted in three solvent environments - water, hexane and cholesterol. Quantifying the values in different solvent environments of a 20 ns MD run, NDM-1 in water registered the highest vibrational flexibility between residue 27 to 32, particularly at residue 31, PHE31, but NDM-1 in hexane registered the most number of vibrational flexibility. NDM-1 in cholesterol is relatively well-ordered compared to water and cholesterol environments. Same with the RMSD, NDM-1 in hexane registered the highest and NDM-1 in cholesterol is relatively stable. The most hydrophilic part of the protein recorded is residue 177, LYS177, which registered 48 water molecules inside the 5 angstrom radius. At residue 31, PHE31, 11 hexane molecules can be found around 5 angstrom radius and in cholesterol system, 7 cholesterol molecules is found at residue 45, GLY45, the highest in the system. Based on the PCA, overall RMSD, and Debye-Waller factors, the rigidity of the protein is increased when solvated in cholesterol.



Methods

Using the crystalline structure PDB ID: 3ZR9 [1], a series of molecular dynamics simulations were performed in three solvent environments: water, hexane, and cholesterol.

Minimization, heating, and equilibration was performed at constant pressure (NPT) of 1 atm. After, twenty nanoseconds (20 ns) constant volume (NVT) production runs at 300 K was performed. The temperature was regulated by Langevin thermostat [2]; bonds with hydrogen atoms was constrained using the SHAKE algorithm [3]; and the long range electrostatic interactions were evaluated using the Particle mesh Ewald method [4].



Conclusion

Different protein conformational changes were uniquely observed in three solvent environments: water, hexane, and cholesterol, after a series of MD simulation production runs. As supported by the PCA, RMSD, and Debye-Waller factor, protein-cholesterol interaction produced the least structural deviation from the starting conformation. On the other hand, protein-hexane interaction registered the highest amount of structural changes in the protein.

An anti-parallel beta-sheet conformation was the most preferred secondary structure in aqueous medium, while the least preferred is the pi-helix structure for the three solvent systems considered. The most hydrophilic part of the protein is observed at residue 177 (LYS177) . In contrast, the most hydrophobic part of the protein is found at residue 31 (PHE31).

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