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In Silico Screening, Identification and Validation of Cryptosporidium hominis Hypothetical Protein and Virtual Screening of Inhibitors as Therapeutics

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Abstract : Computational approaches to predict structure, function and other biological characteristics of proteins are becoming more common in comparison to the traditional methods in drug discovery. Cryptosporidiosis is a major zoonotic diarrheal disease particularly in children, which is caused primarily by Cryptosporidium hominis and Cryptosporidium parvum. Currently, there are no vaccines for cryptosporidiosis and recommended drugs are not effective. With the availability of complete genome sequence of C. hominis, new targets have been recognized for the development of effective and better drugs and/or vaccines. We identified a unique hypothetical epitopic protein in C. hominis genome through BLASTP analysis. A 3D model of the hypothetical protein was generated using I-Tasser server through threading methodology. The quality of the model was validated through Ramachandran plot by PROCHECK server. The functional annotation of the hypothetical protein through DALI server revealed structural similarity with human Transportin 3. Phylogenetic analysis for this hypothetical protein also showed C. hominis hypothetical protein (CUV04613) was the closely related to human transportin 3 protein. The 3D protein model is further subjected to virtual screening study with inhibitors from the Zinc Database by using Dock Blaster software. Docking study reported N-(3-chlorobenzyl) ethane-1,2-diamine as the best inhibitor in terms of docking score. Docking analysis elucidated that Leu 525, Ile 526, Glu 528, Glu 529 are critical residues for ligand–receptor interactions. The molecular dynamic simulation was done to access the reliability of the binding pose of inhibitor and protein complex using GROMACS software at 10ns time point. Trajectories were analyzed at each 2.5 ns time interval, among which, H-bond with LEU-525 and GLY- 530 are significantly present in MD trajectories. Furthermore, antigenic determinants of the protein were determined with the help of DNA Star software. Our study findings showed a great potential in order to provide insights in the development of new drug(s) or vaccine(s) for control as well as prevention of cryptosporidiosis among humans and animals.

Keywords : cryptosporidium hominis, hypothetical protein, molecular docking, molecular dynamics simulation
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