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BSA as a biologically active nanocarriers – computational studies

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Human albumin (HSA) is the main plasma protein that ensures the maintenance of proper osmotic blood pressure and is also involved in the transport of metabolites to cells. It exhibits high solubility at pH = 7.4 and the ability to bind molecules, making it possible to use it as a transporter of drugs such as 5-fluorouracil (5-FU). 5-FU is a drug that causes the incorporation of fluoronucleotides in place of nucleotides that inhibit the thymidylate synthesis of the nucleic acid enzyme. 5-Fluorouracil is used to treat a number of cancers. The biggest problem is its susceptibility to dihydropyrimidine dehydrogenase (DPD), which metabolizes 5FU to the form of dihydrofluorouracil (DHFU) and destroys its therapeutic activity. The crystallographic model of bovine albumin (BSA), which is an equivalent of human albumin (HSA), was selected for the research. Before the docking process, the model was prepared in the Gromacs program. The object was simulated until the conformational changes stabilized, which was monitored via the RMSD function. Finally, the thus obtained BSA model was used for interaction with 5-FU. Before the docking process, the drug was prepared in the Avogadro program. Hydrogens corresponding to a protonation state of pH = 7.4 were added to the drug molecule and minimized in the MMFF94 field using a Conjugate Gradient. The standard protocol of random docking on the whole protein volume was used, the MGLTools tool was used, docked using the rigid Autodock Vin methods. The lowest energy complex was simulated with MD, the drug-free control and the protein/ligand complex were simulated for another 100ns under the same conditions. In the conducted research, the ligand was randomly docked in the entire BSA volume. The results unique for the protein were visualized, and the complex with the most favorable energy was simulated using molecular dynamics methods. BSA has been shown to bind 5-FU at a similar position as HSA in the IB domain. Moreover, it has been established by computational methods that the binding of 5-FU at the center of the protein (IIIA and IIA domains) may be the most common and energetically most beneficial for BSA. Docking at the center with the lowest Gibbs free energy was investigated in detail. Hydrophobic domains inside the ligand-binding pocket have been shown to influence the organization of solvent molecules and the formation of water clusters. The formed clusters constitute the main mechanism that stabilizes the drug inside the canal, which may show promise for its controlled release at elevated temperatures. During the simulation, 5-FU moves into the cavity between domains IIIA and IIA. The binding of 5-FU may affect the mobility of adjacent BSA domains, in particular the IB domain, which is one of the most important pockets for binding substances with therapeutic potential. The presence of the ligand between domains IIIA and IIA resulting in the appearance of strong local chain fluctuations (110-118AA, IB domain).

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