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Original Research article

Study of Interaction of Human Serum Albumin with Doxorubicin (Anti-Cancer Drug) by Docking Simulation

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ABSTRACT

Human serum albumin (HSA) is one of the main endogenous vehicles for biodistribution of molecules by blood plasma. Association constants and thermodynamic parameters for the interaction of HSA with doxorubicin were studied by docking. Docking study suggests that doxorubicin is able to interact with HSA by means of hydrogen bond with one arginine residue, whereas the hydroxyl group is inserted in a hydrophobic pocket. The estimated of Gibbs free energies (ΔG°) is equal to -9.1 kcal/mol for the best model. The negative values of ΔG° indicate a spontaneous process. The association constant value ($Ka \approx 8\times10^3$ $L.mol^{-1}$) is favorable for its efficient biodistribution by blood plasma.

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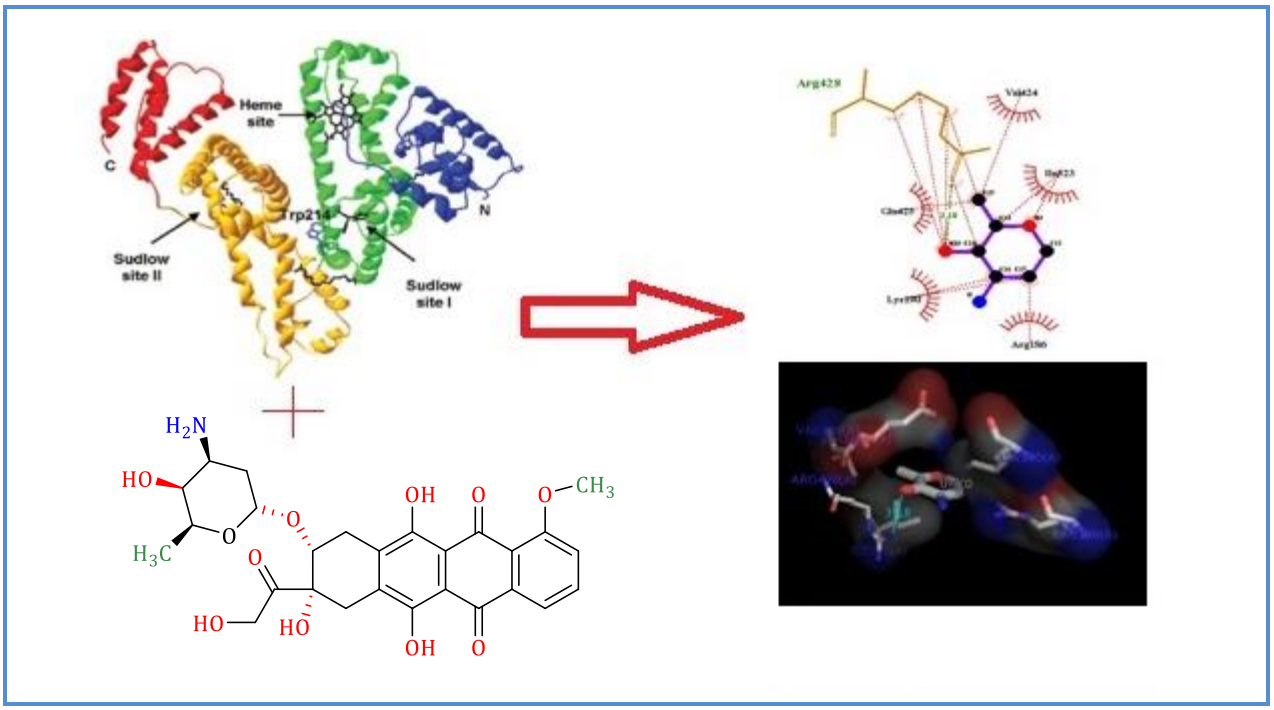
Graphical Abstract



Introduction

Plasma proteins play an important role in the transportation and deposition of substances such as fatty acids, hormones and medicinal drugs in the circulatory system. The interaction of human serum albumin with a wide range of chemically synthesized drugs used in medicine may influence their bioavailability and effectiveness. As a result, several studies have recently focused on revealing the molecular details of these interactions [1, 2]. The interactions between ions and residues in proteins can enhance the stability of some proteins [2-4]. HSA has one cysteine residue at position 34 (in domain I) with a free sulfhydryl group. HSA plays a special role in transporting metabolites and drugs throughout the vascular system. Aromatic and heterocyclic ligands were found to bind within two hydrophobic pockets in subdomains IIA and IIIA (Figure 1), namely site I and site II HSA has a high affinity metal binding site at the *N*-terminus [5-8].

In its unaltered form, doxorubicin has shown great treatment potential, being regarded as one of the most potent of the food and drug administration-approved chemotherapeutic drugs [9]. The ability to combat rapidly dividing cells and slow disease progression has been widely acknowledged for several decades, limited only by its toxicity on noncancerous cells in the human body. The drug is a nonselective class I anthracycline, possessing aglyconic and sugar moieties. The aglycone is comprised of a tetracyclic ring with quinine-hydroquinone adjacent groups, methoxy

substituent short side chain followed by the carbonyl group. The sugar component (also known as daunosamine) is attached to one of the rings by a glycosidic bond. This is comprised of a 3-amino-2,3,4–trideoxy-L-fucosylmoiety [10].

Many studies on the pharmacokinetics of doxorubicin have been conducted assessing the treatment range from single or multi-agent therapy against a range of tumour types. Most of these studies have shown doxorubicin disposition to be multiphasic after intravenous injection. When intravenously infused it is often followed by a triphasic plasma clearance. Doxorubicin's terminal half-life of 24–36 h suggests doxorubicin takes far longer to be eliminated from the tissue than its uptake [9]. Steady-state distribution of the drug is imperative to reduce the risk of toxicity. The range of steady distribution ranges from 500–800 l/m2, and this allows bodily tissues to take up a potent amount of doxorubicin [11]. Doxorubicin and its major metabolite doxorubicinol bind to plasma proteins. In this study, the interaction of doxorubicin with HSA was investigated by docking simulations.

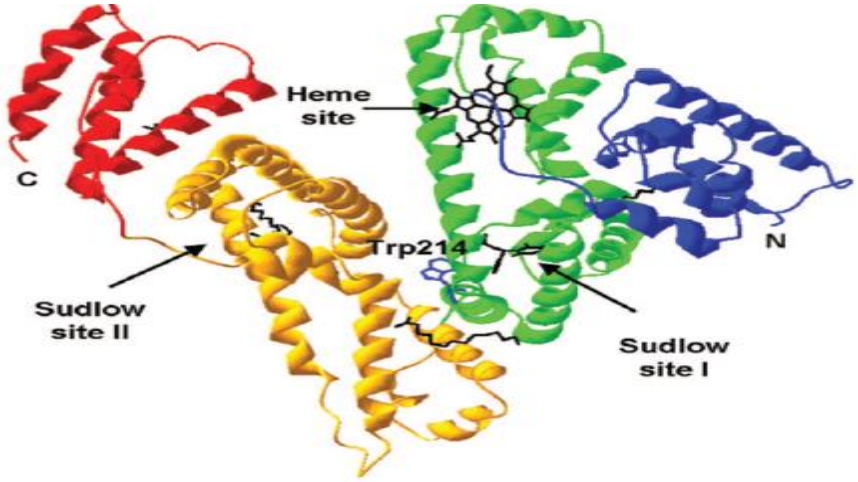


Figure 1. The three-domain structure of HSA. The protein secondary structure is shown in different colors (N and C-termini are marked as N and C, respectively)

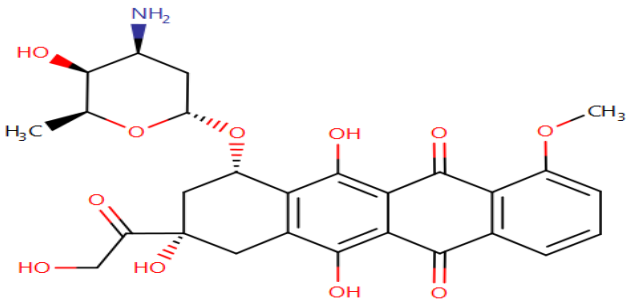


Figure 2. Chemical structural of doxorubicin

Experimental

Doxorubicin docking to HSA was performed with the Auto Dock 4.2 program using the Lamarckian genetic algorithm (LGA). The known crystal structure of HSA (PDB ID:1AO6) was obtained from the Brookhaven Protein Data Bank (PDB http://www.rcsb.org/pdb). Water molecules, ions and ligands co-crystallized with the protein were removed, and hydrogen atoms were added to functional groups with the appropriate geometry within the protein. Kollman united atom partial charges were assigned to HSA and then nonpolar hydrogens of HSA were merged using Auto Dock Tools version 1.5.6. HSA was held rigid and all the torsional bonds of zidovudine are taken as being free in the molecular docking study. During docking calculations, the protein is usually set to be rigid without consideration of the effect of solvent molecules on docking. In order to recognize the binding sites in HSA, blind docking was carried out, the grid size was set to 126×126×126 points with 0.575 Å grid spacing, and the center of the grid was set to 23.96, 39.32, 36.69 Å. The docking parameters used were, GA population size of 150, maximum number of 2.5×107 energy evolutions. A maximum numbers of top 30 conformers were taken into consideration, and the root-mean-square (RMS) cluster tolerance was set to 2 Å.

Result and Discussion

Docking studies provide remarkable information on binding sites of drugs, estimating the binding energies of each drug conformation with corresponding scores and functions. Possible solution obtained by a molecular docking study suggests that doxorubicin is able to interact with HSA by means of hydrogen bonds with one arginine residue, whereas the hydroxyl group is inserted in a hydrophobic pocket (Figures 3 and 4). The estimated of Gibbs free energies (ΔG°) is equal to -9.1 kcal/mol for the best model. The negative values of ΔG° indicate a spontaneous process. The association constant value (Ka ≈ 8×10^{3} L· mol^{-1}) is favorable for its efficient biodistribution by blood plasma.

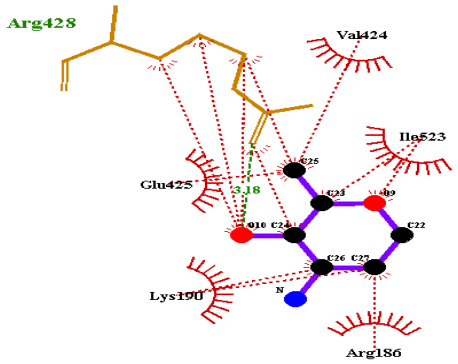


Figure 3. The binding sites of doxorubicin -HSA with the ligplus software

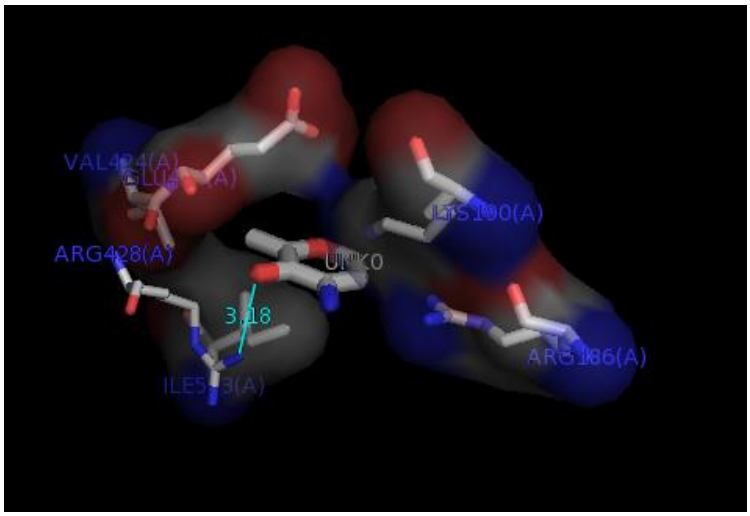


Figure 4. The-binding sites of goxorubicin -HSA with the pymol software

Conclusion

Studies using molecular modeling were performed to analyze the main intermolecular interactions between the doxorubicin and the amino acid residues present in the subdomain IIA interaction cavity. The binding of doxorubicin was accompanied by the increase of polarity within the binding site. Hence, the increase of the surface hydrophobicity results in the decrease of the hydrophobicity in the interior of subdomain IIA. This computational technique can explain the molecular basis of pharmacologically important events that involve binding site recognition on HSA sites II and I in drug displacement.

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