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Docking Studies on the Binding Properties of Methotrexate to Human Serum Albumin

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ABSTRACT

Human serum albumin (HSA) is one of the main endogenous vehicles for biodistribution of molecules by blood plasma. Association equilibrium constants and thermodynamic parameters for the interaction of HSA with Methotrexate were studied by docking. Docking study provides remarkable information on binding sites of HSA with drugs, estimating the binding parameters in some specific places on biomolecules. Docking study suggests that Methotrexate interacts with one lysine, two arginine, one Asparagine and one Glutamine residues, specifically. The Estimated of Gibbs free energies (ΔG°) is equal to -52.67 kJ mol^{-1} for the best model.

Keywords: Human serum albumin, Methotrexate, Docking, Thermodynamic parameters

INTRODUCTION

Plasma proteins play an important role in the transportation and deposition of substances such fatty acids, hormones and medicinal drugs in the circulatory system**.** The interaction of human serum albumin with a wide range of 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]. Methotrexate, MTX, is an inhibitor of tetrahydrofolate dehydrogenase and prevents the formation of tetrahydrofolate, necessary for synthesis of thymidylate, an essential component of DNA (Fig. 1). Disposition and transportation of anticancer drugs by human serum albumin, HAS, affect their bioavailability, distribution and elimination. In this study, the interaction of MTX with HSA was investigated by molecular docking simulations.

Methods

Molecular docking simulation: MTX 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 MTX 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 gred 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.

RESULTS AND DISCUSSION

Docking studies provide remarkable information on binding sites of drugs, estimating the binding energies of the drug every specific place on the HSA. The results obtained by the molecular docking study suggests that MTX interaction with HSA could be something like mean values

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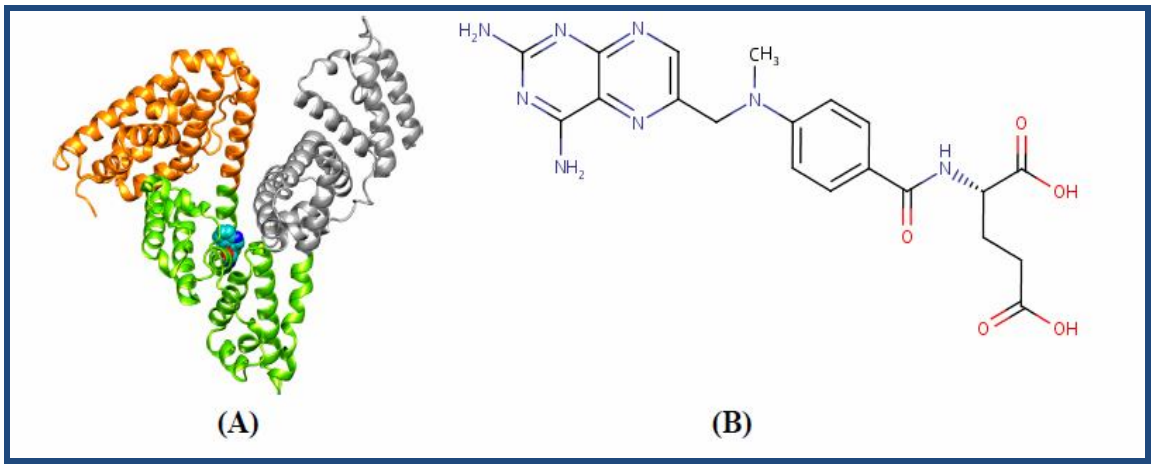

Fig. 1. (A) Crystallographic structure of HSA, showing each of its domains: I (Brown), II (green), and III (gray). Trp214 residue, located in domain II, is presented in the space-filling mode (green); (B) chemical structural of methotrexate.

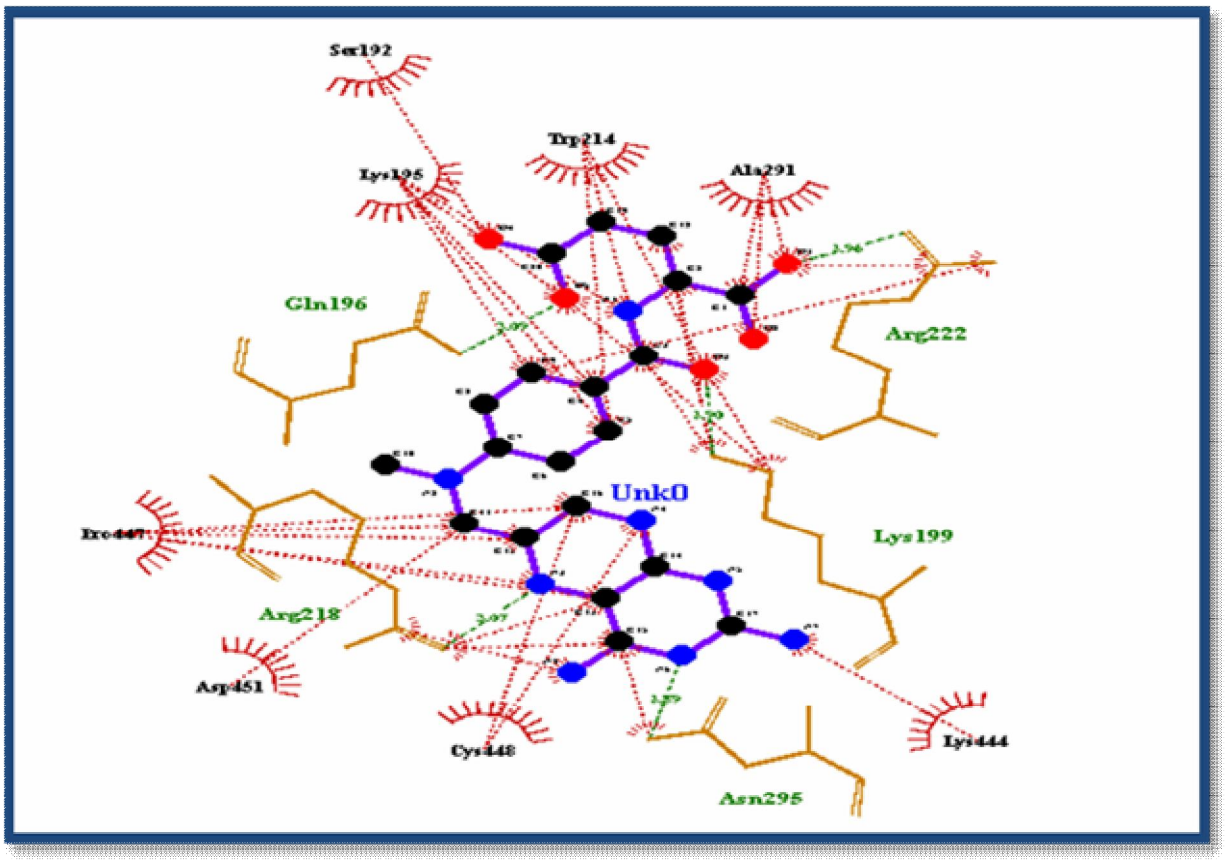

Fig. 2. The binding sites of MTX-HAS is drawn by Ligplus software.

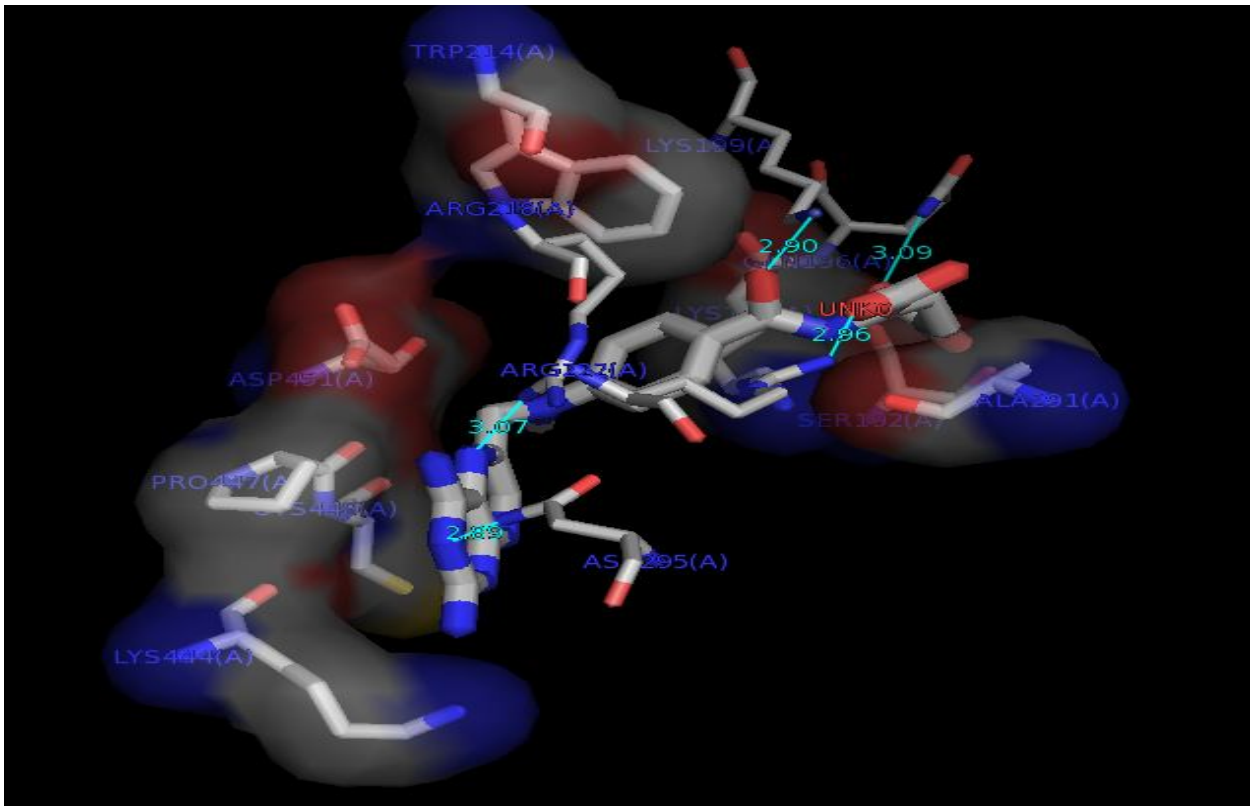

Fig. 3. The binding sites of MTX-HAS is drawn by PyMOL software.

corresponding to MTX hydrogen bonds with one lysine, two arginine, one Asparagine and one Glutamine residues, whereas the carbonyl group is inserted in a hydrophobic pocket, close to Trp-214 (Figs. 2 and 3). The Estimated of Gibbs free energies (ΔG°) is equal to -52.67 kJ mol^{-1} for the best model.

The association equilibrium constant obtained form microcalorimetric method is 110 M^{-1} [9] that is so small value in comparison with huge value of *K*a ≈ 10^9 M^{-1} obtained from Docking results. In order to explain this incompatibility, is that the thermal study shows overall interaction between HSA and MTS, including specific interactions on the certain binding sites and nonspecific interactions in the other places on HSA molecule. Therefore, it is possible to arrive to this collusion that the affinity in specific places revealed by docking, is roughly equal to the affinity of MTX for binding with the rest places on HSA. The fluorescence intensity of HSA decreased regularly and a slight blue shift was observed for the emission wavelength with increasing MTX concentration, indicating that MTX complex could quench the fluorescence of HSA and changes the microenvironment of tryptophan residue. The decreasing of emission intensity of HSA indicates loss of the tertiary structure of HAS [9].

CONCLUSIONS

Human serum albumin (HSA) is composed of a single polypeptide chain of 585 amino acid residues and contains only one Trp residue, Trp-214, located in subdomain IIA. Trp-214 is located at an internal site of the protein with high hydrophobic character. The results obtained by the molecular docking investigation shows that MTX interaction with HSA could be something such as mean value due to MTX hydrogen bonds with one lysine, two arginine, one Asparagine and one Glutamine residues.

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