



Binding behavior of trelagliptin and human serum albumin: Molecular docking, dynamical simulation, and multi-spectroscopy

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ABSTRACT

This study aims to investigate the interaction mechanism of a hypoglycemic agent, trelagliptin (TLP), and human serum albumin (HSA) through computer simulation and assisted spectroscopy methods. Computer simulation including molecular docking and molecular dynamics analysis was conducted under physiological conditions. Molecular docking results indicate that TLP bound to HSA at site I, and the binding behavior was mainly governed by hydrophobic force. Competitive experiments further verified the theoretical conclusion from molecular docking. Molecular dynamics simulation revealed that TLP indeed stably bound to site I of HSA in the hydrophobic subdomain IIA. Moreover, TLP presented a certain effect on the structural compactness of HSA. In molecular dynamics simulation, hydrogen bonds appeared, which suggested the reliability and stability of the combination. The binding energy of the stable phase is around -250 kJ/mol. Fluorescence quenching studies and time-resolved fluorescence analysis indicated that the evident fluorescence quenching phenomenon of HSA could be due to TLP binding initiated by static quenching mechanism. The binding constants (K_b) of the complex were found to be around 10^4 via fluorescence data, and the calculated thermodynamic parameters indicated that hydrophobic force played major role in the binding of TLP to HSA. Synchronous fluorescence and three-dimensional fluorescence results demonstrated that TLP slightly disturbed the microenvironment of amino residues. Circular dichroism spectra showed that TLP affected the secondary structure of HSA. The theoretical and experimental results showed excellent agreement.

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1. Introduction

The interaction between drug molecules and biological macromolecules has been widely studied in interdisciplinary fields spanning biology and pharmacy. Studies on the interaction between drugs and macromolecules have significantly contributed to the understanding of transportation and action processes in the body [1–3].

Human serum albumin (HSA) is one of the most commonly used model proteins in studying interactions between drugs and proteins. In vivo, HSA maintains blood osmotic pressure and binds many endogenous and exogenous molecules, including transport fatty acids, bile pigments, amino acids, steroid hormones, metal ions and many therapeutic molecules. HSA plays an indispensable role as an important carrier for drug efficacy [4,5]. The combination of drug molecule with HSA in different degrees when it enters the blood directly affects the absorption, metabolism, and efficacy of the drug in vivo [6]. The molecular interaction between drug molecules and HSA is a prerequisite for design

and improvement of drugs and will be of great significance in pharmacodynamics, pharmacokinetics, pharmacology, and toxicology [7].

Trelagliptin (TLP, Fig. 1), is a pharmaceutical drug and a once-weekly DPP-4 (dipeptidyl peptidase-IV) inhibitor used for treatment of type 2 diabetes, which has been approved by Japan in March 2015 [8]. TLP controls blood glucose levels by selectively and continually inhibiting DPP-4, the inhibition of DPP-4 increases insulin secretion resulting in the decrease of blood glucose concentration [9]. HSA, as a transport protein, is involved in the entire process of drug action and can help understand the transfer process of TLP by investigating the interaction between TLP and HSA.

Computer simulation, such as molecular docking and molecular dynamics simulation, is a crucial method for drug discovery and development and provides insights into specific molecular mechanisms between proteins and ligands [10,11]. Based on classical physics, molecular dynamics simulation can extrapolate the positions and velocities of each atom at every time interval; data are then analyzed using statistical mechanics to determine other pivotal parameters [11,12]. Molecular dynamics simulation provides in-depth information in understanding the structure and function of biological macromolecules in biological processes or molecular pathways [3,13]. Sudhamalla et al. [14] used molecular dynamics simulation to study the dynamic characteristics of the

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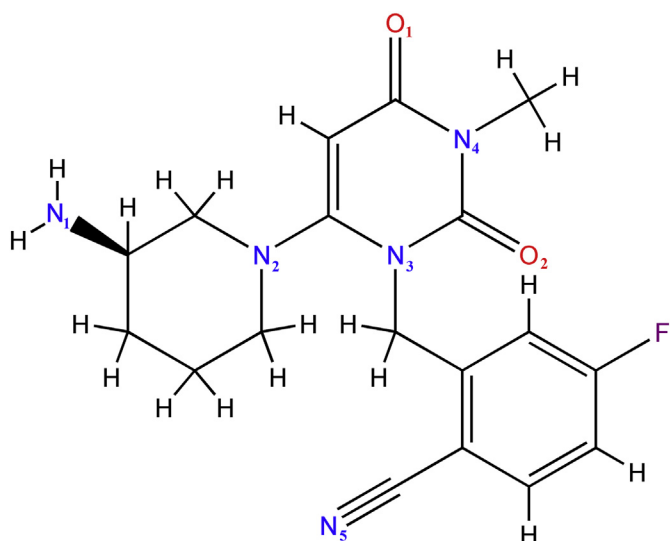


Fig. 1. Molecular structure of trelagliptin.

interaction between HSA and β -sitosterol; the result revealed that β -sitosterol binds to the HSA at drug binding site I stably and leads to conformational changes in HSA. Malleda et al. [15] performed molecular docking and dynamics simulations and reported that betulinic acid bound to HSA and complex system were stabilized around 3500 ps, resulting in conformational changes in HSA.

In this work, the binding mechanism of TLP and HSA was studied through theoretical prediction combined with experimental research. Molecular docking and dynamics simulation were utilized to evaluate the possibility of the combination of TLP and HSA, indicate the binding sites, and investigate the stability of the complex system. The theoretical results are confirmed by the experimental results obtained from fluorescence and circular dichroism spectroscopy methods. This research is helpful to understand the transport mechanism at the molecular level when TLP enters the human body as an inhibitor of DPP-4.

2. Materials and Methods

2.1. Reagents and Chemicals

HSA without essential fatty acids was purchased from Sigma Aldrich (Milwaukee, USA) and used without further purification. Trelagliptin was purchased from Tianjin Heowns Biochem LLC (Tianjin China). Ibuprofen (Ibf), phenylbutazone (Phz), and phosphate buffer were purchased from J&K Scientific Ltd. (Beijing, China). All other reagents were of analytical grade.

2.2. Molecular Docking

The 3D ligand structure of TLP was obtained from PubChem (PubChem CID: 15983988) and the 3D crystal structure of HSA (PDB: 1H9Z) was downloaded from the PDB protein data bank for docking simulation. The molecular docking of HSA with TLP was investigated by YASARA package, version 17.4.17, to explore possible binding modes and active sites using AutoDock VINA docking method and AMBER03 force field. Water and other small molecules were removed during protein preparation. The simulation cell was set automatically around all atoms covering the entire protein. For ligand preparation, the structure was performed with energy minimization using simulated annealing. The pH values for receptor and ligand are equal to 7.40 [10]. The number of a docking run was set to 25. Docking results usually cluster around certain hot spot conformations, and the lowest energy complex in each cluster is saved. Two complexes belong to different clusters if the ligand RMSD is larger than 5 Å. The optimal conformation was selected based on the highest binding energy.

2.3. Molecular Dynamics Simulation

Molecular dynamics (MD) simulation of the complex was performed on YASARA 17.4.17 by using the AMBER14 force field. The structures of HSA and TLP used are the same as structures used in molecular docking. Periodic boundary conditions were applied to system. Counterions were added through randomly replacing water molecules by Na or Cl, which provided a charge-neutral system in 0.9% NaCl solution. The

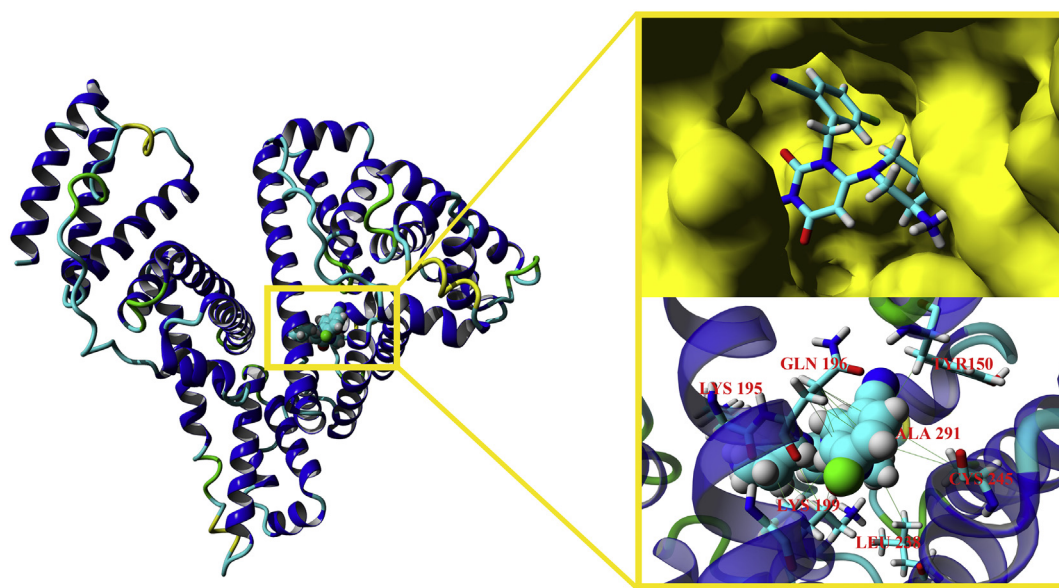


Fig. 2. Molecular docking result of TLP bound to HSA. The yellow color represents the surface of the HSA and the docking pose of TLP (stick model) in site I cavity is shown. The amino acid residues (stick model) were combined with TLP (ball model) by hydrophobic force (green lines) at site I. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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