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Research Article

Molecular Dynamics Simulation for Revealing the Role of Water Molecules on Conformational Change of Human Serum Albumin

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ABSTRACT
Water has an important role in the stability of the structure of the albumin protein. Dehydration condition will affect the conformational changes of albumin protein. This study aims to know the role of water in affecting albumin protein conformational changes by means of molecular dynamics simulations. 3D sample of human serum albumin (1AO6) was obtained from the Protein Data Bank and prepared with VEGAZZ program v.3.08. Simulation process was performed with Gromacs v.4.5.1. The simulation process used the force field GROMOS 43a1 for 1000 ps. The results showed that the dehydration by 30% and 40% can make the dynamics of the protein albumin more static and the dynamic pattern is much different compared to normal conditions. Therefore it can be concluded that the decrease in the amount of water can affect the dynamics of the albumin protein effecting the blood viscosity change.

Keywords: Albumin protein, conformational change, dehydration, water.

INTRODUCTION

The presence of biological water was confirmed in the 1950s from protein structural determined by Perutz. Water is essential to life, yet people still do not fully understand many aspects of its involvement at the molecular level. It plays a wide variety of roles at different levels of complexity, from molecules and cells to tissues and organisms. The above fact shows that water is not simply as a solvent[1-4]. Almost all proteins and nucleic acids are inactive in the absence of water, and hydration determines their structural stability, flexibility and the function[1,2,4]. Specifically for proteins, the dynamics of water–protein interactions govern various activities, including: the facilitation of protein folding, maintenance of structural integrity, mediation of molecular recognition, and acceleration of enzymatic catalysis. Thus, it is important to characterize the dynamic behavior of a biomolecule-associated water – biological water – at the molecular level[2,4]. Preliminary studies indicate that plasma viscosity of normal people became lower by giving the addition of 10 uL of water to 6 ml of plasma, it indicate the function of water on blood rheology. The role of water in affecting the viscosity is might related with conformational dynamic of albumin. Albumin protein acts as a protein transport for various compounds which cover hormones, fatty acids, drugs etc. The aim of the study is understanding the dynamic of albumin conformation in the present of small amount of water. The role of water which can affect the conformation change can be studied with various computational software to perform simulation model of molecular dynamics.

METHODS

Protein Model

3D model of the human serum albumin (HSA) was downloaded from the Protein Data Bank (ID: 1AO6), as protein the result of x-ray diffraction with a resolution of 2.5 A (Figure 1). The model protein was then prepared by removing the ligands presented in the complex, added the missing H atoms using the program of VEGA ZZ 3.05[5].

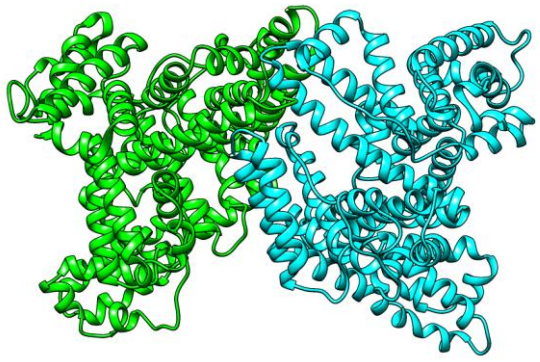

Figure 1: Model 3D of Human serum albumin (1AO6) as protein the result of x-ray diffraction with a resolution of 2.5 A

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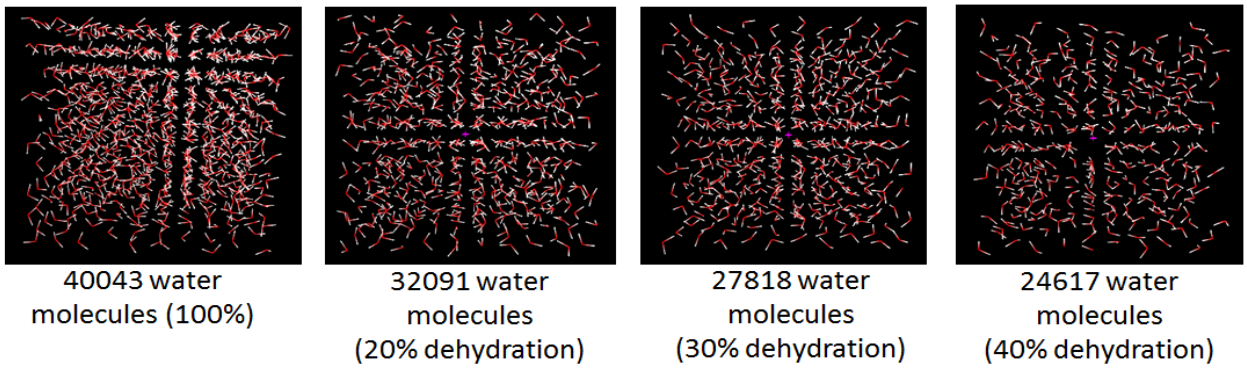


Figure 2: The simulation system on the condition of varies amount of water used normal water conditions (100%), 20% dehydration, 30% dehydration and 40% dehydration

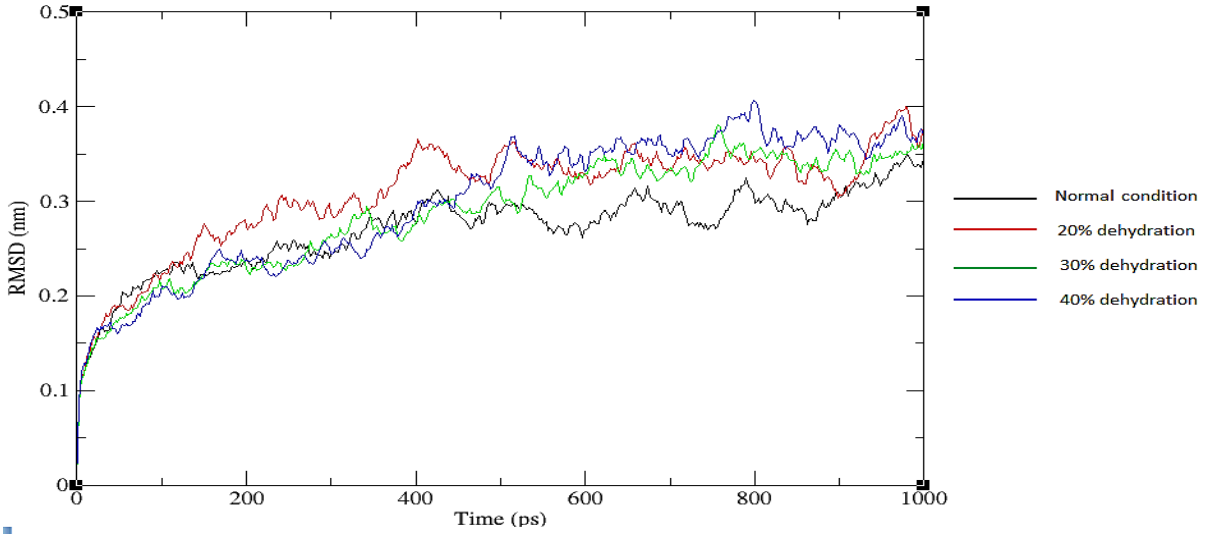


Figure 3: Dynamic change of the human serum albumin conformation in a normal condition (black line), 20% dehydration (red line), 30% dehydration (green line), 40% dehydration (blue line)

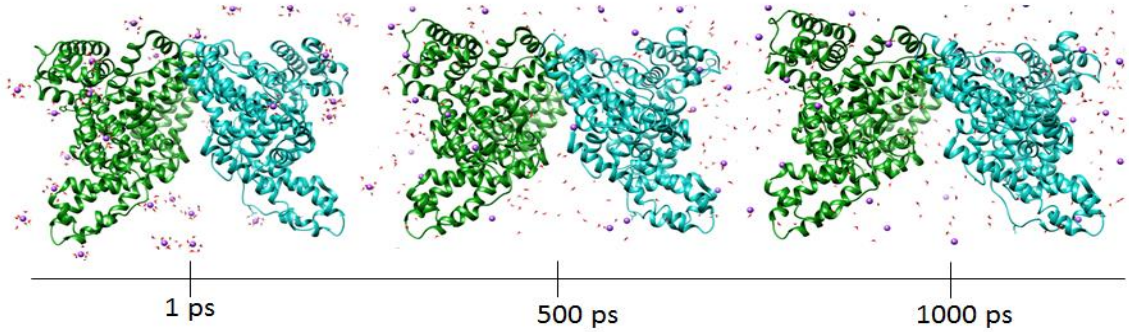


Figure 4: The conformation changes of the albumin protein in a state of dehydration 30%

Hydrophobicity analysis

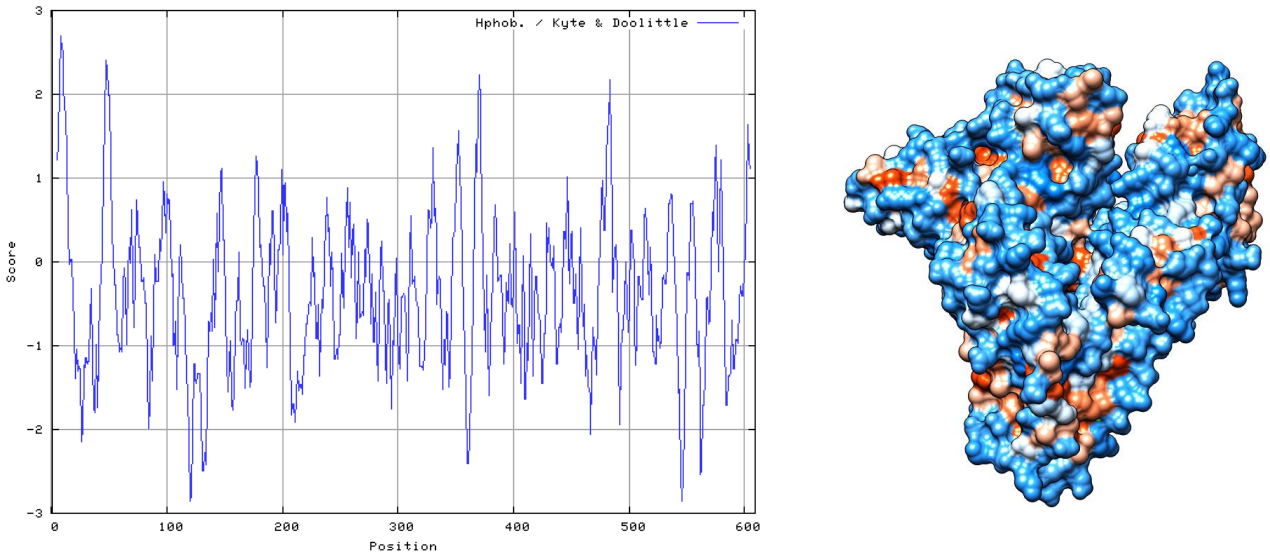
Amino acid properties have important role in protein conformation. We evaluated the hydrophobicity to know the global properties of HAS. Hydrophobicity plot was conducted by ProtScale[6]. The calculation of hydrophibicity surface area was evaluated by Chimera 1.8.1[7].

Molecular Dynamic Simulation

HAS was prepared in a condition of varies amount of water. Changes in the amount of water are a major parameter that will determine the dynamics of conformational changes in albumin. The system used normal water conditions (100%), 20% dehydration, 30% dehydration and 40% dehydration (Figure 2). The first stage of the simulation was minimization process to determine minimum conformation energy of a protein. Minimization process was carried out by using Gromacs v.4.5.1 with force field GROMOS 43a1 and steepest descent algorithm minimization. Minimization process runs for 100 ps to achieve minimal energy of protein[8].

Heating and Equilibration

The second stage in the simulation process was the heating system to match the conditions of a cell, it was 310°K (37°C). This heating process run for 100 ps till



a b

Figure 5: Hydrophobicity of human serum albumin (HSA). (a) Hidrophobicity plot of HAS and (b) Hydrophobics Surface Area

achieving the balance conditions with the program of Gromacs v.4.5.1. Equilibration process was done by the system of Number, Volume and Temperature and Number, Pressure and Temperature to ensure a stable temperature and pressure.

Production Run

The simulation process to know the changes of the dynamics of the protein could be conducted after equilibrium condition, it was after 100 ps, and the simulation process lasted 1000 ps with Gromacs program v.4.5.1. The simulation results were analyzed by Root Mean Square Deviation (RMSD) to know global conformational changes of albumin protein.

Visualization of biomolecules

Molecular dynamics results were visualized using Chimera v.1.81[7].

RESULT AND DISCUSSION

Computational study showed that there is the conformational change of HSA by a reduction in water ranging from 20%, 30% and 40%. Conformational changes in the HSA does not exceed more than 2 A, it means that change in conformation of HSA, is still within the normal ranges and it is not damaging the structure of the HSA. Differences change of the albumin structural dynamics begin on the condition of 30% dehydration, it can be seen from the pattern of the dynamics that are much different from the normal. It is signed by not having much fluctuation on RMSD. Less dehydrated albumin namely 20% dehydration show dynamic pattern approaching normal condition. While the simulation of 40% dehydration showed similar results with 30% dehydration (Figure 3). It indicated that the 30% dehydration may changes of hydrophobicity bonding patterns of internal albumin molecules structure, as simulated on figure 4 and 5. Results showed that the protein movement is more static marked by the simulation process to 1500 and 1000ps and there no significant changes. The simulation results can strengthen the hypothesis that the presence of water is very important in influencing the conformation of the albumin protein. Decreasing the number of water molecules would have an impact on protein stability. The less amount of water showing the conformational dynamics is not too fluctuating it may be explained why the serum albumin have high viscosity under dehydrated condition, and might reversible by addition amount of water[1,2,4,9,10]. HSA conformational changes are affected by the number of water molecules[2]. The polarity of the water molecules produces hydrogen bonds, so the tugging between hydrogen and water molecules or other hydrophilic molecules occurs. The tugging between water molecules and HSA causes conformational changes. The role of water is very important in the stability and structure of the protein. It is associated with nature of hydrophobic from protein[2,4]. Based on hydrophobicity analysis of human serum albumin (Figure 5). It showed that global properties of human serum albumin is more hydrophilic, but some amino acid have high hidrophobicity properties. This condition provide favorable interaction of water with human serum albumin. When the water meet hidrophilic surface area, it can cover all protein surface region. However, the protein has hydrophic surface that is not favorable to interact with water molecule. It can affect directly to dynamic movement of protein when there are reducing number of electrons on the surface, causing the less water interaction that might induce the conformational change of albumin[2-4,11]. Conformational changes depend upon several things, namely the curvature of the albumin, smooth or rough surface layer HSA, as well as the nature of hydrophobic and hydrophilic membrane surface HAS[2,12]. The important role of water in determining the pattern of conformational changes in the protein albumin can be used as a basis for water therapy in some diseases (diabetics, cancer, malaria) with the aim of lowering blood viscosity[11,13,14].

CONCLUSION

Molecular dynamics simulations reveal the phenomenon of water influence on conformational dynamics of the albumin protein. Dehydration condition of 30% and 40% showed dynamics patterns which are much different from normal conditions. It proved that water has an important role in determining blood viscosity which directly affects the albumin protein in the blood. This study became the basis that the first step for the treatment of primary prevention of any diseases affecting blood rheology.

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