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Glycation-mediated binding defect in human serum albumin transport of erdosteine: implications in diabetes

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Abstract

Human serum albumin (HSA) is a protein in human blood primarily responsible for transporting ligands. Erdosteine is an important drug used in the treatment of acute and chronic respiratory diseases. This study employed molecular docking and molecular dynamics simulation methods to investigate the interaction between erdosteine and HSA. In the presence of glucose, the binding energy of erdosteine decreased, indicating reduced binding affinity. Docking results suggested changes in the interaction sites and binding residues, with the preferential binding site shifting in the presence of glucose. Molecular dynamics simulations showed increased fluctuations when glucose was present. The solvent-accessible surface area of all HSA systems remained stable under physiological conditions, with a slight decrease over time. Analysis of secondary structural changes indicated stable erdosteine binding with no alteration in HSA's secondary structure. Hydrogen bonding analysis showed a decrease in hydrogen bond formation between erdosteine and HSA in the presence of glucose; since hydrogen bonding is crucial for ligand-protein interactions, this reduction is significant. Principal component analysis indicated that HSA's flexibility was not affected by erdosteine binding, even in the presence of glucose. Electrostatic interactions played a key role in erdosteine binding to HSA, with Arg 218 contributing the highest energy in the complex under glucose conditions. Elevated glucose levels in diabetic patients can induce structural and functional changes in proteins, potentially impacting the effective management of coexisting clinical conditions. Such changes may affect drug binding to transport proteins, thereby altering drug efficacy, clearance, and therapeutic outcomes.

Keywords: Human serum albumin, Erdosteine, Molecular docking, Molecular dynamic simulation, Glucose.

1. Introduction

Human serum albumin (HSA) is an extensively studied protein present in human blood, involved in the transport of ligands of both intrinsic and extrinsic origin [1]. HSA plays an important role in the transport of ligands in blood, serving as a key transport protein for a wide variety of molecules, including drugs, vitamins, minerals, and fatty acids [2]. HSA is the most abundant protein in human plasma and performs various functions, including scavenging reactive oxygen species. It also helps maintain oncotic pressure. HSA acts as a carrier for free fatty acids, hormones such as T3 and T4, and steroid hormones like cortisol and estradiol. Additionally, HSA assists in the transport of vitamins A, D, E, and K [3]. HSA also plays an important role in the blood transport of various ions and metal complexes, such as zinc and copper, helping to maintain their homeostasis. Additionally, HSA contributes to colloid osmotic pressure and the regulation of fluid balance. Proper transport of molecules is important for ensuring proper distribution of nutrients and waste products between tissues and affects their excretion. The physiological importance of HSA can be estimated by its role in several medical conditions originating from changes in HSA levels. HSA plays a significant role in transporting a varied range of substances through the bloodstream, contributing to metabolic processes, drug distribution, and fluid balance [4,5]. Hydrophobic molecules cannot easily dissolve in the watery environment of the blood. HSA serves as a carrier for these hydrophobic molecules, allowing them to travel through the bloodstream to the tissues where they are needed. This function is critical because without HSA, these molecules would not be able to circulate efficiently. Many therapeutic drug molecules, including anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs), and chemotherapeutic agents, bind to HSA. HSA acts as a reservoir for the molecules. Drug binding to the transport protein helps in controlling the active drug concentration in the bloodstream. HSA is a multifunctional protein

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important in many physiological processes, like maintaining metabolic balance and drug pharmacokinetics. Drug binding affects the therapeutic efficacy and toxicity of the molecule. Drugs bound to albumin are often considered pharmacologically inactive, as only the free (unbound) form can interact with target receptors [6, 7].

Erdosteine is a mucolytic agent. This molecule is chemically classified as a thiol derivative. It is produced for the management of chronic obstructive bronchitis symptoms [8]. Sulfhydryl groups of erdosteine are removed after phase-I in hepatic metabolism. Metabolites of erdosteine show both mucolytic activity and scavenging activity against free radicals [9]. Erdosteine modulates mucus by regulating its production and altering its viscosity, which enhances mucociliary transport in the airways. It has a positive effect on expectoration by breaking disulfide bonds in mucus glycoproteins, making mucus less thick and easier to expel. Additionally, erdosteine inhibits free radicals generated by cigarette smoke, contributing to its antioxidant activity [10, 11]. A chronic obstructive lung disease (COPD) patient study has indicated that erdosteine is safe and well-tolerated during treatment [12]. Mild and infrequent gastrointestinal events have been reported during treatment with erdosteine [13, 14]. Erdosteine is widely used for treatment of respiratory diseases like bronchitis [15]. It is known to bind to albumin and be transported in the blood. However, the effect of glycation on the transport of erdosteine in human blood is not well understood. Therefore, understanding the effect of increased glucose in diabetes on the transport of drugs in human blood is important for the development of effective therapies for various diseases. Glycation of proteins is a non-enzymatic, spontaneous chemical reaction of reducing sugars like glucose with the amino groups of proteins [16, 17]. Hyperglycaemia is elevated blood sugar levels and contributes to the formation of advanced glycation end products (AGEs). Hyperglycaemia develops in uncontrolled or untreated diabetes. Glycation begins when a reducing sugar reacts with the free amino groups of proteins like lysine or arginine residues, forming Schiff base. The Schiff base rearranges over time to form a more stable intermediate like N-ε-fructosyl lysine. Amadori products undergo further complex chemical reactions, forming advanced glycation end products. These advanced glycation end products are highly reactive and can modify proteins irreversibly [18,19]. Covalent modification of proteins can alter the protein structurally and functionally. Glycation, which impairs normal physiological functions, is a major cause of various conditions associated with hyperglycemia, including damage to the eyes, kidneys, and heart. Uncontrolled diabetes can lead to inflammation and oxidative stress because advanced glycation end products (AGEs) bind to specific cellular receptors on different cell types, such as endothelial cells, immune cells, and neurons. This interaction triggers signaling pathways that contribute to the progression of diabetic complications [20]. Glycation has also been implicated in cancer. Advanced Glycation End Products can promote the malignant transformation of cells, stimulate tumor growth, and enhance metastasis [21]. Glycation is a natural process; its effects can be minimized by Blood Sugar Control, Dietary Modifications and therapeutic medication. Regular physical activity helps the body use insulin more effectively and can lower blood glucose levels. Exercise also supports cardiovascular health and weight management [22]. The effects of glycation are wide-ranging, affecting tissue function and contributing to a number of chronic diseases and the aging process [23]. Glycation causes structural changes in proteins, which can lead to misfolding or denaturation and the formation of cross-links between proteins. In the vascular system, cross-linking of collagen in the blood vessel walls results in increased stiffness, contributing to hypertension, atherosclerosis, and reduced blood flow to tissues [24].

Protein glycation-mediated modifications in protein structure can impair drug transport, particularly in the context of elevated blood glucose levels. HSA has multiple binding sites for various molecules, and glycation alters the binding affinity of these sites. Major ligands such as fatty acids, bilirubin, hormones, and therapeutic drugs are significantly affected by glycation-induced changes in HSA [25]. Altered drug binding due to glycation could lead to suboptimal drug delivery and therapeutic failure.

Molecular docking is an important tool to study the binding of glucose to different sites on a transport protein. The glucose interaction with the amino acids of the protein can be identified, and it becomes possible to see how glycation can alter accessibility and affinity for other ligands. Molecular dynamics (MD) simulations are a powerful computational tool giving valuable insights into the conformational changes, flexibility, and dynamics of proteins. Molecular dynamics simulations offer an opportunity to study glycation-induced changes in protein structure and function. By simulating the effects of glycation on protein conformation, binding interactions, and protein stability, MD simulations can provide critical insights into how glycation affects biological processes at the molecular level. This approach can help uncover the underlying mechanisms behind diabetes-related protein dysfunction and complications while offering valuable information for the development of therapeutic strategies aimed at preventing or reversing the effects of glycation.

2. Materials and methods

2.1. Molecular docking

The interaction between erdosteine and HSA was observed through molecular docking study. Protein Data Bank (PDB ID: 4IW2) corresponding to HSA's three-dimensional crystal coordinates was employed. This protein file contains one glucose molecule in its crystal structure. The structure of erdosteine, corresponding to PubChem database (CID: 65632), was saved. AutoDock Vina was the tool used for molecular docking. Two molecular dockings were performed, one with HSA containing glucose and other without glucose. In glucose-absent docking, all non-protein atoms, such as glucose, water, and other atoms, were removed. In glucose present docking, all non-protein atoms were removed except glucose. In all instances where glucose is present in the docking, HSA is denoted as HSA(+glu). The preparation of HSA for docking was carried out using AutoDockTools version 1.5.6. This program demanded the addition of polar hydrogen atoms and Kollman charges. After this, the structure in PDBQT format was saved. The grid used for docking was defined and spacing of 1 Å was chosen. Grid dimensions were 86×64×78 Å. The grid was centered at coordinates x = 2.578, y = 0.112, and z = 17.006. To enhance flexibility, AutoDockTools 1.5.6 was used to set the rotatable bonds in erdosteine, making them flexible during docking. The

subsequent analysis was performed using Discovery Studio 2024 and PyMOL.

2.2. Molecular dynamics simulation

The stability and dynamics of the protein ligand complex were studied employing GROMACS 2018 for molecular dynamics (MD) simulation study [26]. Four independent simulations were conducted. The first simulation involved apo HSA, which refers to HSA alone in water without any bound ligands. Second, HSA with erdosteine, abbreviated as HSA-erdosteine complex. Third, HSA with glucose bound, abbreviated as HSA (+glu). Fourth, HSA with glucose and erdosteine, abbreviated as HSA (+glu)-erdosteine complex. The topology for HSA was generated in GROMACS 2018 using the pdb2gmx utility. The topology for ligands (glucose or erdosteine) was created using the Antechamber package in AmberTools [27]. To simulate the protein/complexes, Amber99sb-ILDN force field was utilized [28]. Topologies of the ligand and protein to form complex were manually combined. To ensure periodic boundary conditions, structures were enclosed in triclinic boxes. The distance of 10 Å was maintained from the box edges. The TIP3P water model was used for solvation. Charges were neutralized by adding counter ions (Na+ or Cl-), and 150 mM NaCl was added to mimic physiological conditions. Energy minimization was performed for up to 50,000 steps. Energy minimization removes weak Van der Waals interactions. Two equilibration sets were run before the main simulation. The first equilibration was performed using the NVT ensemble at 310 K for 500 ps with a V-rescale thermostat [29]. The second equilibration was performed using the NPT ensemble at 1.0 bar for another 500 ps with a Parrinello-Rahman barostat [30]. The equilibrated systems were then subjected to a 100 ns simulation with periodic boundary corrections applied to all trajectories before analysis. Analyses were conducted using GROMACS utilities. The binding energy constituents were estimated using the MM-PBSA method by the g_mmpbsa package [31].

2.3. Statistical analysis

The principal component analysis (PCA) tool provided with the molecular dynamics package was used. PCA is a multivariate statistical technique employed to gain insight into the flexibility of the protein chain in both the absence and presence of ligand molecules.

3. Results

3.1. Molecular docking

Two molecular docking of erdosteine were performed. One with HSA and another with HSA(+glu). The docked complex is shown in Fig. 1A.

In the docking of erdosteine with HSA(+glu), the ligand was not found in Sudlow's site I, as this site was already occupied by the glucose. Erdosteine was docked outside of subdomain IIA. The docked complex of erdosteine with HSA(+glu) is shown in Fig. 1B.

3.2. Molecular dynamics simulation

Molecular dynamics (MD) simulations were utilized to study complexation of erdosteine with HSA. This study helps to investigate the stability and dynamics of the protein in the absence or presence of glucose. The root mean square deviation (RMSD) values of the trajectories so obtained are reported in Fig. 2A.

Secondary structure was accessed to look into the impact of the binding of erdosteine on the structural stability of HSA. Secondary structure analysis was conducted.

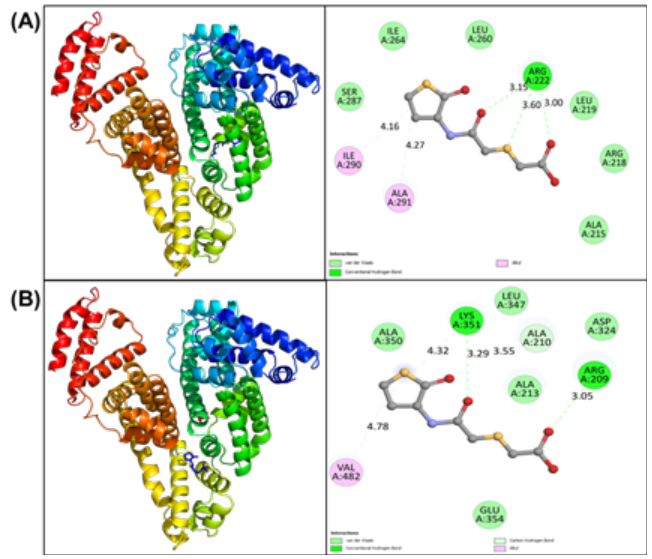

Fig. 1. (A) Docked complex of erdosteine with HSA. (B) Docked complex of erdosteine with HSA(+glu).

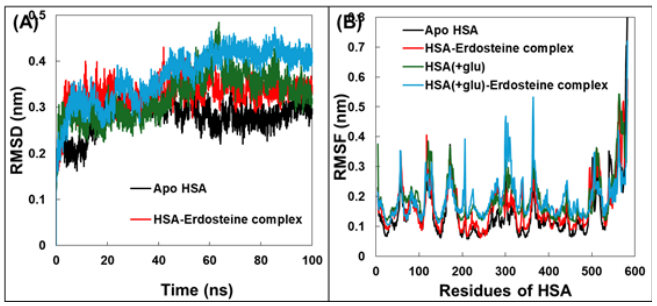

Fig. 2. (A) Root mean square deviation (RMSD) of the backbone atoms of apo HSA, HSA-erdosteine complex, HSA (+glu), and HSA (+glu)-erdosteine complex during 100 ns molecular simulation. (B) Root mean square fluctuation (RMSF) of the alpha carbon atoms of residues of HSA or HSA(+glu) in the absence and presence of erdosteine. Root mean square fluctuation (RMSF) of all HSA residues was calculated as shown in Fig. 2B. To increase a profound understanding of the stability of HSA, the radius of gyration (R_g) and solvent-accessible surface area (SASA) were examined.

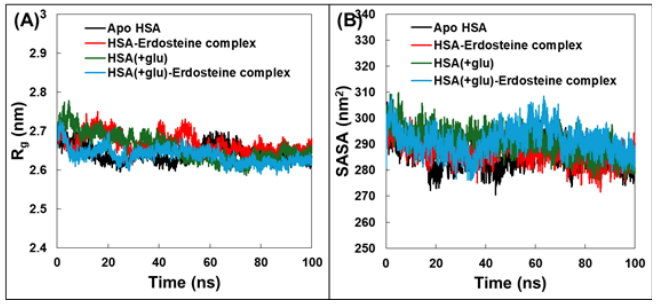

Fig. 3. (A) Radius of gyration (Rg) of the backbone atoms of apo HSA, HSA-erdosteine complex, HSA(+glu), and HSA(+glu)-erdosteine complex during 100 ns molecular simulation. (B) Solvent accessible surface area (SASA) of apo HSA, HSA-erdosteine complex, HSA(+glu), and HSA(+glu)-erdosteine complex during 100 ns molecular simulation.

For the apo HSA, the average percentage of coils, bends, turns, α-helices, and 3-helices was 13.181, 7.765, 14.295, 61.451, and 3.221, respectively (Fig. 4A).

Principal component analysis (PCA) is a statistical method. This method was employed to assess the flexibility of HSA both with and without ligand [40]. Fig. 5A illustrates the projection of eigenvectors in a two-dimensional space for HSA both with and without ligand.

MM-PBSA calculations were employed for studying the energetics of the interaction between erdosteine and HSA (Fig. 6A).

Primary energy-contributing residues for the erdosteine and HSA interaction were identified with MM-PBSA analysis, as shown in Table 1.

4. Discussion

4.1. Molecular docking

The interaction of erdosteine with HSA or HSA(+glu) was examined using molecular docking techniques. Two sets of molecular docking experiments were performed. The docked complex is shown in Fig. 1. One with HSA-Fig. 1A and another with HSA(+glu), Fig. 1B. The molecular docking with HSA resulted in a binding energy of -5.6 kcal/mol, while the binding energy with HSA (+glu) was -4.9 kcal/mol. A clear decrease in binding energy shows that the affinity of erdosteine towards HSA decreased when glucose was present. In glucose-absent docking (Fig. 1A), erdosteine interacted at subdomain IIA of HSA (commonly referred to as Sudlow's site I). The ligand formed hydrogen bonds with Arg222. The complex was also stabilized by hydrophobic interactions (Ile290 and Ala291) and Van der Waals forces (Ser287, Ile264, Leu260, Leu219, Arg218, and Ala215). In the docking of erdosteine with HSA (+glu), the ligand was not found in Sudlow's site I, as this site was already occupied by the glucose. Erdosteine was docked outside of subdomain IIA. The docked complex of erdosteine with HSA(+glu) is shown in Fig. 1B. In this docking, erdosteine formed hydrogen bonds with Lys351, Arg209, and Ala210. The complex was also stabilized by one hydrophobic interaction, Val482 and many Van der Waals forces with Als350, Leu347, Ala213, and Asp324. Overall, the molecular docking results show that the preferential binding site of erdosteine in HSA is changed when glucose is present in the system.

4.2. Molecular dynamics simulation

Molecular dynamics (MD) simulation methods were used to study the stability and dynamics of erdosteine with HSA in the absence and in the presence of glucose. Figure 2A reports the root mean square deviation (RMSD) values of the trajectories. The RMSD for apo HSA increased until around 20 ns before stabilizing, a trend also seen in the HSA(+glu)-erdosteine complex. However, it took longer (around 60 ns) for the trajectory of HSA(+glu) to become equilibrated. A similar result was obtained for HSA(+glu)-erdosteine complex. The average RMSD values for apo HSA, HSA-erdosteine complex, HSA(+glu), and HSA(+glu)-erdosteine complex were 0.280, 0.327, 0.324, and 0.368 nm, respectively. To analyse fluctuations in structure, the root mean square fluctuation (RMSF), as shown in Fig. 2B, of all HSA residues was calculated. RMSF Values below 0.2 nm for most HSA residues, suggesting minimal structural fluctuations. In the case of apo HSA and HSA-erdosteine complex, almost all residues exhibited fewer fluctuations. However, for HSA(+glu) and HSA(+glu)-erdosteine complex, the fluctuations were slightly higher. The average RMSF for apo HSA, HSA-erdosteine complex, HSA(+glu), and HSA(+glu)-erdosteine complex was 0.132, 0.154, 0.182, and 0.178 nm, respecti-

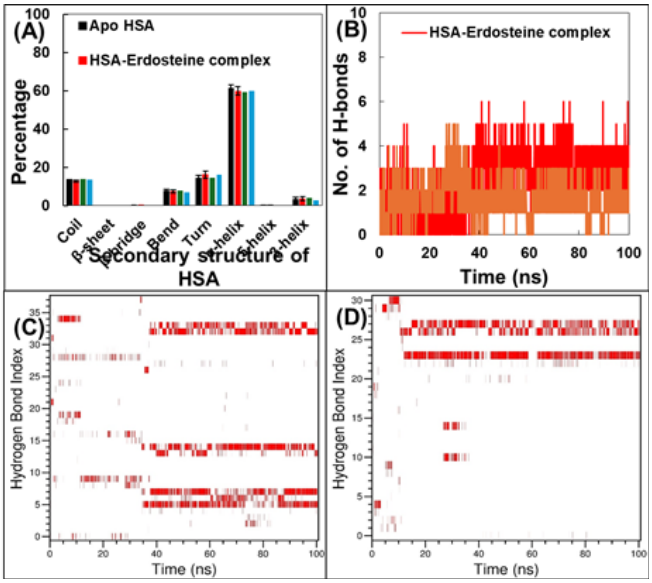

Fig. 4. (A) Percentage of secondary structures in HSA or HSA (+glu) in the absence and presence of erdosteine. (B) Number of hydrogen bonds formed by erdosteine with HSA or HSA(+glu) for a 200 ns molecular simulation. (C) Hydrogen bond existence map for the HSA-erdosteine complex. (D) Hydrogen bond existence map for the HSA(+glu)-erdosteine complex.

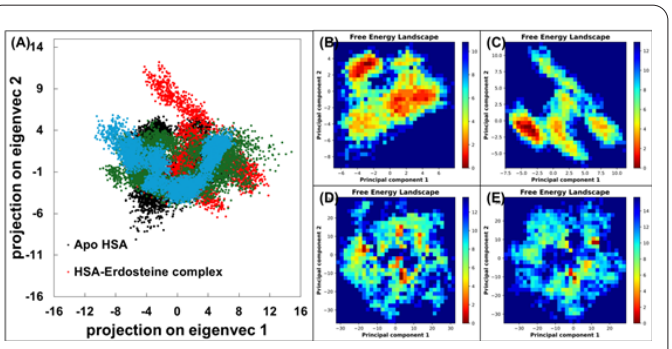

Fig. 5. (A) Projection of eigenvectors of apo HSA, HSA-erdosteine complex, HSA(+glu), and HSA(+glu)-erdosteine complex. (B) Free energy landscape of apo HSA. (C) Free energy landscape of HSA-erdosteine complex. (D) Free energy landscape of HSA(+glu). (B) Free energy landscape of HSA(+glu)-erdosteine complex

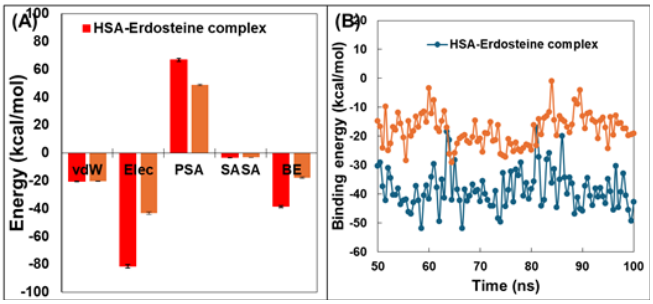

Fig. 6. (A) Different constituents of binding energies for the interaction of erdosteine with HSA and HSA (+glu). (B) HSA and HSA (+glu), their energy per frame data for the interaction of erdosteine

Table-1. Major energy contributing residues of HSA and total energies for the interaction of erdosteine with HSA and interaction of erdosteine with HSA(+glu) obtained from MM-PBSA calculations.

HSA-erdosteine complex			
Residues	**Polar Energy**	**Apolar Energy**	**Total Energy**
Arg218	7.900±0.157	-0.166±0.005	-7.454±0.197
Arg222	1.305±0.087	-0.049±0.003	-3.347±0.133
Lys199	8.167±0.208	-0.083±0.003	-2.922±0.171
Lys195	0.231±0.212	-0.025±0.005	-1.510±0.111
Glu153	17.022±0.365	-0.157±0.005	-1.307±0.190
Leu238	0.056±0.007	-0.106±0.004	-1.062±0.039
Glu285	0.754±0.024	0.000±0.000	-0.760±0.023
Arg336	0.143±0.010	0.000±0.000	-0.734±0.017
Arg348	0.125±0.008	0.000±0.000	-0.726±0.02
Ala291	-0.187±0.033	-0.15±0.005	-0.652±0.052
Lys444	0.040±0.003	0.000±0.000	-0.635±0.033
Leu219	0.005±0.006	-0.048±0.002	-0.625±0.032
HSA(+glu)-erdosteine complex			
Residues	**Polar Energy**	**Apolar Energy**	**Total Energy**
Glu153	13.295±0.308	-0.18±0.003	-3.125±0.147
Glu188	0.736±0.036	0±0	-1.374±0.023
Asp451	0.051±0.01	0±0	-0.85±0.018
Ala291	0.714±0.035	-0.19±0.005	-0.842±0.04
Ile290	0.277±0.017	-0.1±0.003	-0.822±0.029
Phe156	-0.08±0.028	-0.033±0.003	-0.77±0.063
Ile264	0.05±0.005	-0.047±0.002	-0.637±0.02
Leu260	-0.102±0.009	-0.07±0.002	-0.619±0.028
Glu292	0.177±0.042	0±0	-0.524±0.037
Glu184	0.099±0.004	0±0	-0.517±0.007
Asp187	0.132±0.006	0±0	-0.512±0.006
Leu238	0.004±0.004	-0.072±0.003	-0.447±0.015

100 frames taken from 50 to 100 ns of the trajectory at equal intervals were used for MM-PBSA calculations.

vely. It can be said that the presence of glucose increases the fluctuation in residues of HSA. To increase the understanding of the stability of HSA in various situations, the radius of gyration data was analysed. Radius of gyration (R_g) and solvent-accessible surface area (SASA) were analysed to give insight into the protein stability. Compact and globular proteins exhibit minimal changes in their radius of gyration during simulations [32]. Open and expanded proteins show greater variations in radius of gyrations. The radius of gyration is an essential indicator of the structural compactness and stability of a protein in simulation studies. Fig. 3A depicts the R_g of all systems over time. Throughout the simulations, apo HSA showed only minor variations. Similar results were obtained for HSA-erdosteine complex, HSA(+glu), and HSA(+glu)-erdosteine complex. The average R_g values for apo HSA, HSA-erdosteine complex, HSA(+glu), and HSA(+glu)-erdosteine complex were 2.642, 2.667, 2.657, and 2.636 nm, respectively. Similarly, SASA of all HSA systems remained stable when simulated under physiological conditions, with a slight decrease over time (Fig. 3B). The average SASA for apo HSA, HSA-erdosteine complex, HSA(+glu), and HSA(+glu)-erdosteine complex were 285.441, 287.213, 291.072, and 291.148 nm^2, respectively.

Secondary structure analysis is important to assess the structural stability of HSA in various conditions. For HSA alone, without glucose, the average percentages of different structural elements were calculated as follows: coils (13.181%), bends (7.765%), turns (14.295%), α-helices (61.451%), and 3_10-helices (3.221%), as shown in Fig. 4A. All of these secondary structural components remained roughly unchanged in case of HSA-erdosteine complex, HSA(+glu), and HSA(+glu)-erdosteine complex systems. For instance, the average percentage of coils, bends, turns, α-helices, and 3-helices in HSA-erdosteine complex was 12.803, 7.406, 16.215, 59.876, and 3.681, respectively. This shows the consistency in secondary structural components, which suggests that erdosteine binding with HSA or HSA(+glu) does not adversely affect the protein's structure [33-37].

The hydrogen bonding between erdosteine and HSA was further explored (Fig. 4B). On average, erdosteine forms approximately 2.462 hydrogen bonds with HSA, while the ligand forms 1.718 hydrogen bonds. The data clearly show that the presence of glucose in the system reduces the average number of hydrogen bonds formed between erdosteine and HSA. Throughout the trajectory, the consistency of hydrogen bonds was maintained, as depicted in the hydrogen bond profile (Fig. 4C & D). For the HSA-erdosteine complex, hydrogen bonds were more frequent compared to the HSA(+glu)-erdosteine complex. The occupancy of hydrogen bonds within the complexes

was also analyzed. Arg218 showed the highest consistency for erdosteine binding with HSA. The occupancy rate was more than 40%. In the binding of erdosteine in another case with HSA(+glu). The residue in HSA, Arg257, was the most consistent one. This has an occupancy rate of over 65% throughout the simulation study. It validates that hydrogen bonds significantly contribute to the stabilization of ligand compounds when complexed with HSA [38, 39]. Principal component analysis (PCA) is a statistical method. This method was available as a tool with a simulation package; the PCA method was employed to assess the flexibility of HSA both with and without ligands during simulation studies [40]. Figure 5A demonstrates the estimate of eigenvectors in a two-dimensional space. The results showed a similar 2D conformational space of the eigenvectors, which signifies that the binding of erdosteine either to HSA or HSA(+glu) did not affect the HSA's flexibility during simulation. Generated eigenvectors were then utilized to create the free energy landscape (FEL), as shown in Fig. 5B-E. As observed, all trajectories reached energy minima, but the locations of these minima vary across the complexes. For apo HSA, two energy minimum points were identified, whereas the HSA-erdosteine complex exhibited three energy minimum points. The data also indicate a slight increase in the flexibility of HSA following complexation with erdosteine.

MM-PBSA calculations were employed to study the energetics of the interaction between erdosteine and HSA (Fig. 6A). Non-covalent interactions like hydrophobic forces, van der Waals interactions, electrostatic forces, and hydrogen bonds are crucial in ligand-protein complex formation and its stability over time [41]. For erdosteine binding to HSA, electrostatic interactions were found to be the most prominent non-covalent interaction (-20.546 kcal/mol), followed by Van der Waals interactions (-81.311 kcal/mol). The binding of the erdosteine to HSA (+glu) was primarily mediated by electrostatic forces (-20.266 kcal/mol) and Van der Waals interactions (-43.230 kcal/mol). There was an observation that minor contributions from SASA energy, while polar solvation energy mainly affected the overall interaction of the ligand in both situations. The total binding energies for the interaction of erdosteine with HSA and HSA(+glu) were found to be -38.473 and -17.765 kcal/mol, respectively. The data further validate that erdosteine has a high affinity towards HSA when glucose is absent in the system. Primary energy-contributing residues for the erdosteine and HSA interaction were recognised with MM-PBSA analysis, as shown in Table 1. Arg218 was the highest energy-contributing residue. It is followed by Arg222, Lys-199, Lys195, Glu153, Leu238, Glu285, Arg336, Arg348, Ala291, Lys444, and Leu219 in complexation of erdosteine with HSA. In the HSA(+glu)-erdosteine complex, the main contributors were Glu153, Glu188, Asp451, Ala291, Ile290, Phe156, Ile264, Leu260, Glu292, Glu184, Asp187, and Leu238. (Fig. 6B) reports the energy per frame data calculated for 100 snapshots from 50 ns to 100 ns. It is observed that the energy per frame data remained stable throughout this period. Energy per frame data did not show significant fluctuations. For the HSA-erdosteine complex, the minimum and maximum energy per frame were -51.925 kcal/mol and -17.039 kcal/mol, respectively. For the HSA(+glu)-erdosteine complex, the minimum and maximum energies were -29.060 kcal/mol and -0.971 kcal/mol, respectively. These differences in energy values are attributed to the movement of the ligand at the binding site as it approaches the target protein.

Human serum albumin (HSA) is an abundant monomeric protein in human blood plasma, primarily synthesized in the liver. As the major transporter protein in the blood, HSA plays a crucial role in carrying various endogenous and exogenous molecules, including hormones, fatty acids, bilirubin, and drugs. Diabetes is characterized by an uncontrolled hyperglycemic state and is frequently complicated by chronic obstructive pulmonary disease (COPD). Erdosteine is an important drug for managing COPD, making its interaction with HSA particularly relevant in diabetic patients.

4. Conclusion

In this study, the binding of erdosteine to HSA was investigated both in the presence and absence of glucose. It was observed that the presence of the compound reduced erdosteine binding, altered the preferential binding site, and changed the participating residues. Molecular dynamics simulations revealed increased fluctuations in HSA when glucose was present. The solvent-accessible surface area of HSA remained stable under physiological simulation conditions, with only a slight decrease over time. Erdosteine binding caused no significant alteration in the secondary structure of HSA. However, hydrogen bond formation between erdosteine and HSA decreased in the presence of glucose. Principal component analysis of chain flexibility showed that HSA's overall flexibility was not affected by erdosteine binding under the studied conditions.

The decreased binding of erdosteine in the presence of glucose is clinically significant. High glucose levels in the blood during diabetes can induce structural and functional changes in transport proteins like HSA, affecting drug binding and transport. These modifications can alter the pharmacokinetics and pharmacodynamics of drugs, impacting their efficacy, clearance, and ultimately the treatment outcomes. This is especially important in diseases such as diabetes, where multiple clinical manifestations coexist, necessitating polypharmacy, which further complicates drug binding and transport processes.

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Conflict of interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

No human or animals were used in the present research.

Informed consent

The authors declare that no patients were used in this study.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

Mohammd Rehan Ajmal, Fahad M Almutairi, Rizwan Hasan Khan and Imadeldin Elfaki: Research design and supervision; Nada Mahmoud Al-Atawi, Ohud Muhammed Ahmad Al-Harbi, Rasha Sulaiman Muhammad Al-Finaikh, Sheakha Ahmad S Al-Balawi: Perform all laboratory procedures

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