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MOLECULAR DOCKING OF GLYCYRRHIZIN WITH 11β-HSD1 PROTEIN

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Abstract. Carried out in the paper molecular docking has shown that glycyrrhizin, a biologically active glycoside from the roots of licorice Radices glicerrhizae, binds to the enzyme 11ß hydroxysteroid dehydrogenase -1(11ß-HSD1), which in the liver causes a decrease in the concentration of cortisol in hepatocytes and at the same time increases lipid metabolism and decreases the process of gluconeogenesis. The binding of glycyrrhizin to the 11ß-HSD1 protein occurs symmetrically at the boundary of two subunits, and the amino acid residues Ser227, Asp228, Thr231, His233 of one polypeptide chain (chain A) and Ser166 residues of another chain (chain B) participate in the formation of polar (hydrogen) bonds. The hydrophobic interactions involve six residues, such as Leu114, Trp146, Gly199, Glu224, Thr230, Ile232 from subunit A and Val97, Glu100, Lys164, Gln165, Met169, Thr 170 from subunit B. The complex of glycyrrhizin and protein 11β-HSD1 has an affinity of -9.7 kcal/mol, whereas in the case of the complex of glycyrrhizin and subunit A of protein 11β-HSD1 it is equal to -9.1 kcal/mol. The same value in the case of glycyrrhizin and subunit B of protein 11β-HSD1 is equal to -8.1 kcal/mol.

Keywords: *molecular docking, glycyrrhizin, 11β-HSD1 protein, 11β-HSD2 protein, gluconeogenesis, SARS-CoV.*

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1. Introduction

The rapid development of molecular biology has made it possible to identify biological molecules that affect the development of certain diseases. This has given a new direction for the search for medicinal compounds, which molecules should selectively bind to biological target molecules. Nowadays, due to the development of computer technologies for drug development, along with the experimental methods for searching for biologically active molecules that selectively bind to target macromolecules, such as proteins, molecular modelling methods are being increasingly used (Davis & Morris, 1991).

According to the standards of rational drug development, a biologically active molecule must selectively bind to a certain region of a biological macromolecule, its active site, which is involved in the development of the disease, thereby affecting the course of the disease (Khan *et al*., 2013). Biologically active molecules can be inhibitors and agonists, antagonists and modulators of protein receptors.

Molecular docking refers to methods of structure-oriented drug development. The work of docking programs is based on reducing the positioning of the ligand in the active

center of the biological target and estimating the free energy of protein-ligand binding. The higher this energy, the more likely that in experiments this ligand will bind to the target protein, and the more effective the new drug based on such an inhibitor will be, since a lower concentration of the drug will lead to a therapeutic effect (Mammadova *et al*., 2013).

Research using glycyrrhizin, which is a calcium and potassium salt of tribasic glycyrrhizic acid found in licorice roots (Radices glicerrhizae), as a ligand is a priority due to its wide range of activities and presence of a number of biological targets (Davis & Morris, 1991).

The effect of GA on the endocrine system is manifested by glucocorticoid and mineralocorticoid activity. Inhibition of the enzyme 11β hydroxysteroid dehydrogenases -1(11β-HSD-1) in the liver causes a decrease in the concentration of cortisol in hepatocytes along with the increase in lipid metabolism and a decrease in the process of gluconeogenesis (Wang *et al*., 2015).

It is well known that glucocorticosteroids (GCS) affect the distribution of adipose tissue in the human body. A number of studies have shown that obese patients have hyperactivation of the 11β-HSD1 enzyme in adipose tissue and hepatocytes, a key enzyme that stimulates the conversion of metabolically inactive cortisone to active cortisol (Fig. 1) (Pereira *et al*., 2012; Morgan *et al*., 2014).

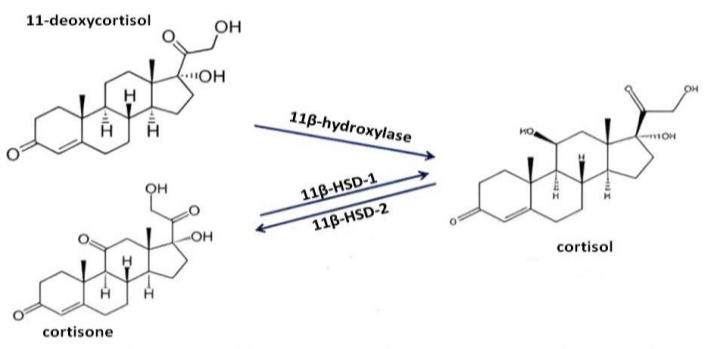

Figure 1. Interconversion of cortisone and cortisol

In contrast, 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2), which catalyzes the conversion of cortisone to cortisol, had a lower expression (Balachandran et al., 2008). As mentioned earlier, it has been suggested that 11β-HSD1 activity may be one of the pathogenic mechanisms underlying the development of the metabolic syndrome. Data from experimental animal studies have shown that selective 11β-HSD1 overexpression in adipose tissue (similar to that observed in obese patients) led to the development of the metabolic syndrome, in particular, dyslipidemia, obesity and hypertension associated with activation of the renin-angiotensin-aldosterone, insulin resistance and impaired carbohydrate metabolism. In addition, adipocytes had a large size, than usual. The main effect was observed in visceral adipose tissue, possibly due to a higher density of glucocorticosteroid receptors (Bujalskaet *et al*., 2002; Masuzaki *et al*., 2001; Wamil & Seckl, 2007). The data obtained made it possible to consider 11b-HSD1 as a new target for pharmacotherapy. The aim of our work is to perform molecular docking of glycyrrhizin as a ligand and 11β-HSD1 target protein.

2. Materials and methods

The molecular docking was performed on the protein 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1), which was downloaded from the Protein Data Bank, and the glycyrrhizin ligand from the Drug Bank in 3D. We open the 11β-HSD1 protein in the Discovery studio program (https://discover.3ds.com/discovery-studio-visualizer-download), then remove water molecules, add hydrogen bonds and save the molecule in the pdb format.

Glycyrrhizin ligand, downloaded from the Drug Bank in 3D, is opened using the Chimera program (https://www.cgl.ucsf.edu/chimera/download.html), the structure is minimized, and saved in the pdb format. After preparing the ligand and protein, molecular docking using the AutoDock Vina program (https://vina.scripps.edu/download) was performed and the data were indicated below:

receptor = 1xse.pdbqt
ligand=ligand3.pdbqt
out = vin.pdbqt
center_x = 25.885146
center_y = 41.140844
center_z = 28.746344

Molecular docking by the Autodock-Vina method, structure minimization, and subsequent analysis were performed as described previously [9]. The dissociation constants of glycyrrhizin complexes were calculated by the formula KD = exp (ΔG / RT), where KD is the dissociation constant of complexes, ΔG is the binding energy of glycyrrhizin, R is the gas constant equal to 1.986 cal/mol, T is the absolute temperature in Kelvin (298 K).

The molecular docking method was performed using the Autodock 4.2 program (Scripps Research Institute, www.scripps.edu). AutoDock uses the Lamarckian genetic algorithm to find the minimum free energy configuration of the protein-ligand complex. The protein is considered as a rigid structure, while rotation around single bonds is allowed in the ligand.

This program has proven itself in many studies, including the docking of ligands to steroid receptors (Mammadova et al., 2013).

3. Results

The results of the molecular docking of 11β-HSD1 glycyrrhizin to protein complexes are shown in Table 1.

Table 1. The results of the molecular docking of 11β-HSD1 glycyrrhizin to protein complexes

Structure	Affinity, kcal/mol	Estimated dissociation constant of the complex, mkm
The complex of glycyrrhizin and 11β-HSD1 protein	-9.7	0.026
The complex of glycyrrhizin and protein 11β-HSD1 subunit A	-9.1	0.00034
The complex of glycyrrhizin and protein 11β-HSD1 subunit B	-8.1	0.039

Data preparation and analysis of the results were carried out using various software that is freely available for academic use. To prepare the ligand and protein structures for the docking, the referenced above software was used.

The binding of glycyrrhizin to the 11β-HSD1 protein (Fig. 2) occurs symmetrically at the boundary of two subunits, and the amino acid residues Ser227, Asp228, Thr231, His233 of one polypeptide chain (A chain) and the Ser166 residues of the other chain are involved in the formation of polar (hydrogen) bonds (circuit B). Hydrophobic interactions involve six residues from each subunit, such as Leu114, Trp146, Gly199, Glu224, Thr230, Ile232 from subunit A and Val97, Glu100, Lys164, Gln165, Met169, Thr 170 from subunit B

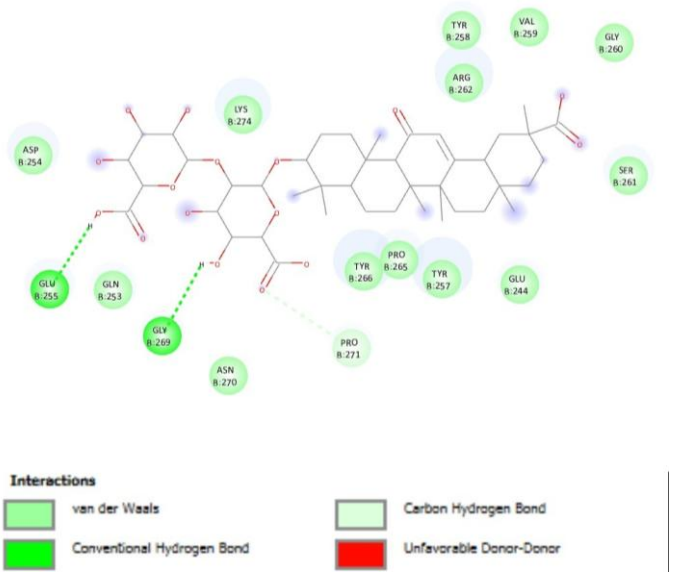

Figure 2. Binding of glycyrrhizin to the 11β-HSD1 protein by the corresponding amino acids

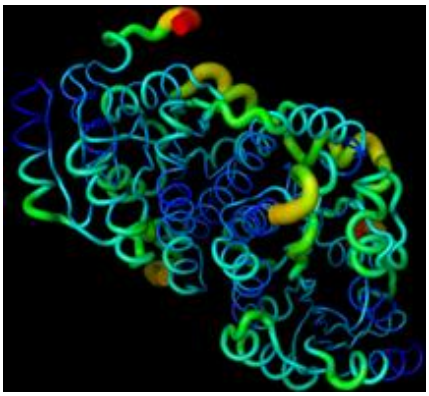

Figure 3. Subunits A and B of the 11β-HSD

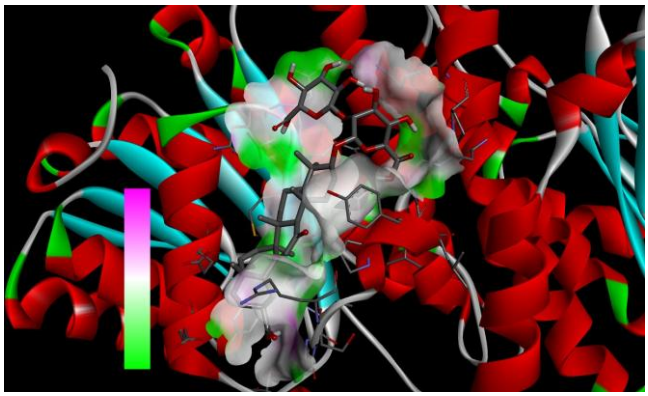

Figure 4. Molecular docking of glycyrrhizin with the 11β-HSD1 protein

As a result of docking for glycyrrhizin, scoring functions such as binding energy, intermolecular energy and inhibition constant characterizing the interaction of glycyrrhizin and 11β-HSD protein were obtained. The lipophilicity constant, based on the quantum chemical parameters obtained by the Gaussian 03 program using the corresponding equations, was calculated and was equal to 2.5. The Gaussian network

model (GNM) method (Morgan *et al*., 2014) was used to assess the change in protein backbone mobility as a result of cofactor binding. This method is based on a simplified model that represents a protein as a network of connected nodes, the interaction between which is described by a harmonic potential and makes it possible to estimate the mobility of amino acid residues based on the structure of the protein.

The molecule of the 11β-HSD protein with subunits A and B (Fig. 3) and the molecular docking of the protein with the glycyrrhizin ligand (Fig. 4) were given below.

4. Conclusion

The results of molecular docking show that the probability of affinity of a ligand molecule for a protein in a complex with two subunits (affinity -9.7) is greater than with subunits separately (affinity of subunit A-9.1, subunit B-8.1).

The binding site of the 11β-HSD1 protein consists of amino acids (Ser227, Asp228, Thr231, His233 of one polypeptide chain and Ser166 residues of another chain) that form hydrogen bonds with the oxygen atom of the carboxyl groups of glycyrrhizin.

Glycyrrhizin, being a triterpene saponin with diverse biological functions and pharmacological activities, has been widely used as one of the potential drugs against COVID-19, as it was active against SARS-CoV in vitro (Cinatl *et al*., 2003). Moreover, unlike corticosteroids, which have also been used in the treatment of COVID-19, glycyrrhizin does not have immunosuppressive properties, but rather enhances the immune response. In the future, by converting glycyrrhizin, it is possible to create new anti-SARS-CoV drugs with increased activity (Xu et al., 2018). Considering the experience and lessons learned from the fight against SARS, glycyrrhizin is a promising drug and deserves further research in combination with the 11β-HSD1 protein, which regulates the level of corticosteroids in the human body.

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