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Docking studies of the chemical components of the composition of *Bupleurum aureum* plant in relation to hepatoprotective biotargets

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ABSTRACT

With the purpose of searching the objective parameters of dependence of the activity of Bupleurum aureum plant on the components of its chemical composition and determining the possible mechanisms of the hepatoprotective effect the docking studies have been conducted by the method of a flexible molecular docking using the SCIGRESS software package. The results obtained allow making the assumption that the most likely mechanism of the hepatoprotective effect is inhibition of protein (code 2I9T), it may be associated with the presence of flavonoids (quercetin), alcohols (xylitol) and monoterpenoids (lolioside) in the composition of Bupleurum aureum plant.

Keywords: molecular docking, hepatoprotective activity, Bupleurum aureum

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INTRODUCTION

Currently preference is mostly given to natural drugs, mainly of the plant origin, due to their availability and fewer side effects. The lack of knowledge concerning the mechanism of their action is one of the main obstacles for wider clinical use of medicinal plants. Taking into account the experience in relation to components of their chemical composition, knowledge of the mechanism of action of medicinal plants can be obtained using molecular docking. There are plenty of methods of molecular modeling focused on solving various problems and distinguished by both a strategic approach and implementation. Molecular docking (or molecular combining) is one of the method for molecular modeling, which allows to provide agonism/antagonism to the biological target selected and the most favourable orientation for formation of a stable complex and the position of one molecule (ligand) in relation to another molecule (target) [1,2]. Docking allows to reduce expenses and time due to carrying out the procedure that is similar to high-performance biological screening. Knowing the spatial structure of the target (receptor or enzyme) and the spatial structure of the ligand it is possible to explain the mechanism of interaction between them at the molecular level and calculate the strength of binding between them (affinity) [3]. Affinity is equal to the concentration of the ligand, in which half of the targets binds with the ligand [4-6]. The measure of the biological activity is such ligand concentration at which the cell response is equal to half the maximum. Therefore, ligands with the highest affinity provided will block or activate the molecular target in biological experiments best of all [7-9]. Affinity of the ligand in relation to the receptor is assessed both by geometric criteria of surface complementarity of the ligand in relation to the cavity of the receptor and by physico-chemical criteria (formation of hydrogen bonds, electrostatic interactions, Van der Waals repulsion, etc.).

The aim of docking is the search of the most suitable positions and orientations of the ligands in the ligand binding centre (LBC) of the receptor or enzyme, as well as identification of factors that may lead to improvement of the ligand-receptor interaction. The result of the simulation is conformation of the ligand, which interacts with the protein binding site in the best way [10-11].

Preliminary pharmacological screening has been allowed to choose *Bupleurum aureum* as object of our research. This material row protects liver from any kind of poisoning, damage effect of carbohydrates, petrochemical plants

emissions, and protects also from consequences of radioactive radiation [12]. It shows hepatoprotective, antioxidative and immunomodulatory activities, general health-improving effect on organism, promotes metabolic process improvement [13-15]. We think this raw material may be used for preventive maintenance and treatments diseases of hepatobiliar system.

MATERIALS AND METHODS

Docking studies were conducted by the method of a flexible molecular docking using the SCIGRESS software package (Fujitsu, Fukuoka, Japan (license 742F6852C191)) in order to search the parameters of dependence of the activity of *Bupleurum aureum* plant on the components of its chemical composition and determining the possible mechanisms of the hepatoprotective effect [16,17].

The stages of conducting molecular docking with the help of the SCIGRESS software package were as follows [18]:

1. The choice of biotargets and determination of their active sites.
The choice of biotargets was stipulated by the literature data on the mechanism of the hepatoprotective effect [19]. The structure of proteins of the redox-sensitive transcription factor – NFkB (nuclear factor kappa B) (code 1VKX) (code 2I9T), which activation resulted in apoptosis or necrosis of hepatocytes was chosen from Protein Data Bank (PDB) [20].

After adding hydrogen atoms to the protein molecule of NFkB factor (nuclear factor kappa B) (code 1VKX) and isolation of chain B the active site containing residues of such amino acids as PHE353, ARG354, PHE355, ARG356, TYR357, GLU360, GLY361, PRO362, SER363 , HIS364, GLY365, GLY366, LEU367, PRO368, SER410, LEU411, VAL412, GLY413, LYS414, PHE434 , ALA435, ASN436, LEU437, GLY438, ILE439, LEU440 was isolated (Fig.1).

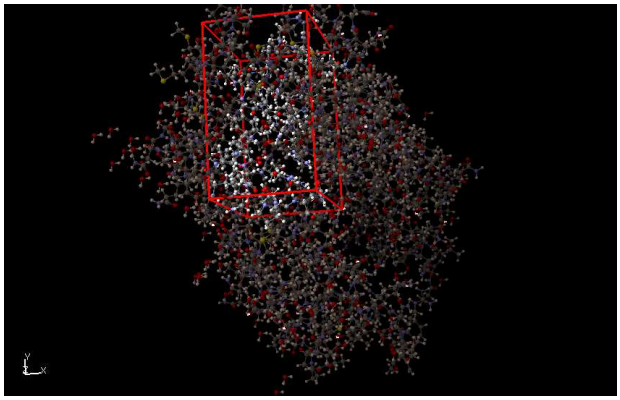


Fig. 1. The active site of the NFkD factor protein (nuclear factor kappa B) (PDB code 1VKX)

Similarly the active site for the protein (PDB code 2I9T) has been determined (Fig. 2)

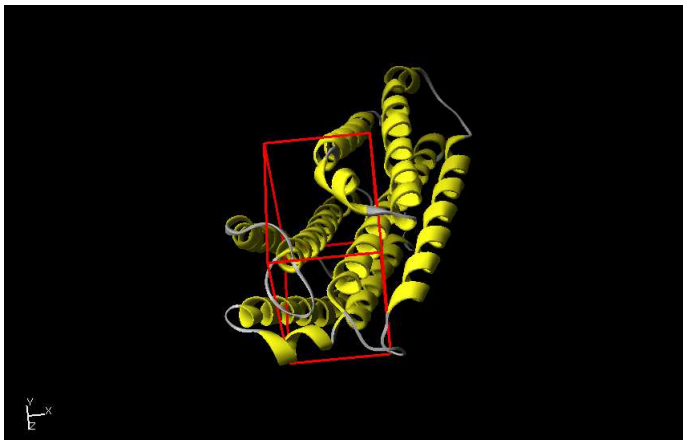


Fig. 2. The active site of the protein (PDB code 2I9T) (a crystallographic model in the form of ribbons)

2. Conducting 3D optimization of the chemical structures in the composition of *Bupleurum aureum* plant (the MM3 molecular mechanics method).

All structures included in the chemical composition of *Bupleurum aureum* plant were designed using the ISIS DROW 4.0 software and saved as .mol. files. Then these structures were imported into the SCIGRESS software and saved in csf. format (Fig. 3).

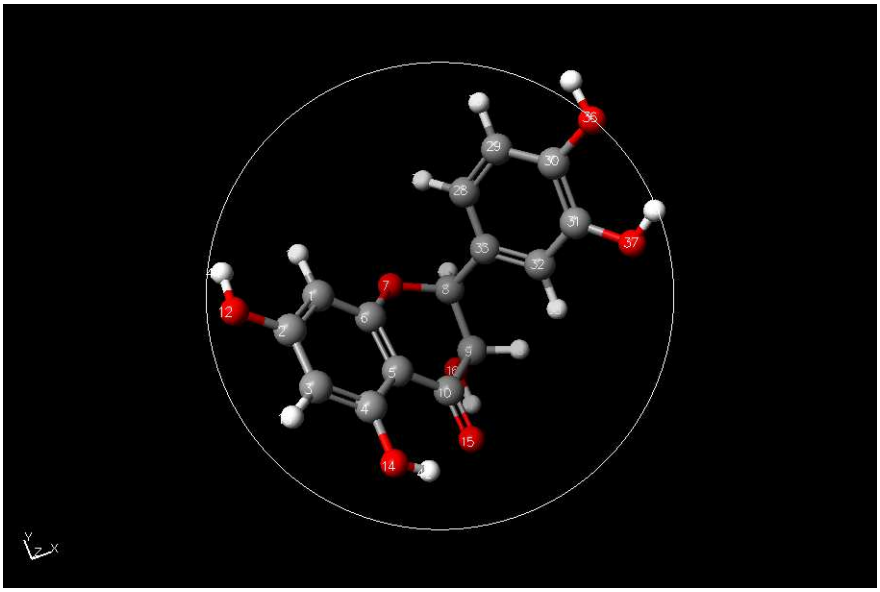


Fig. 3. The chemical structure of quercetin in csf. format (prior to optimization)

The next step was the optimization of all structures by the MM3 molecular mechanics method (Fig.4).

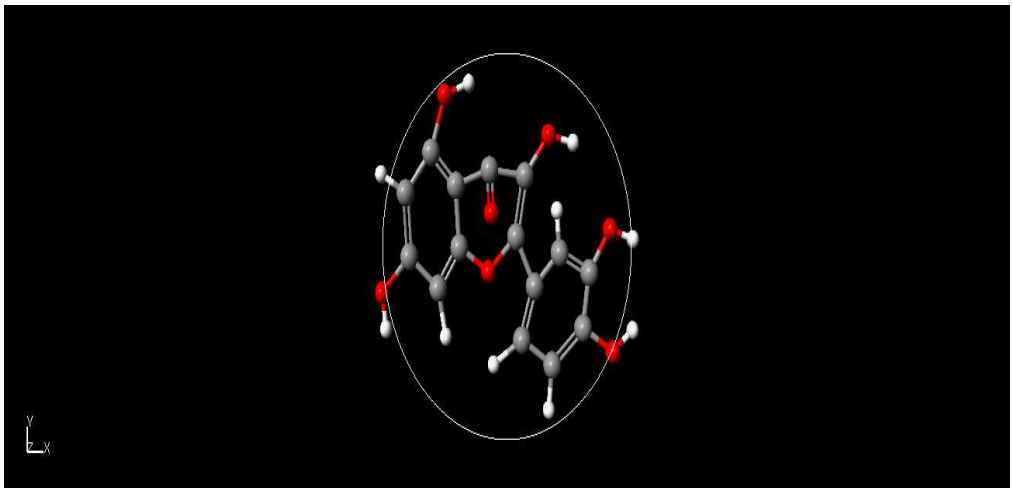


Fig. 4. The chemical structure of quercetin after optimization by the MM3 method

3. Conducting 3D molecular docking.

The molecular docking was conducted for all chemical structures in the composition of *Bupleurum aureum* plant using the “Dock into active site” function (Fig. 5a and 5b). When carrying out the automatic docking a genetic algorithm (GA) was used. The genetic algorithm is an evolutionary algorithm of search used for solving problems of optimization and simulation by sequential selection, combination and variation of the parameters studied.

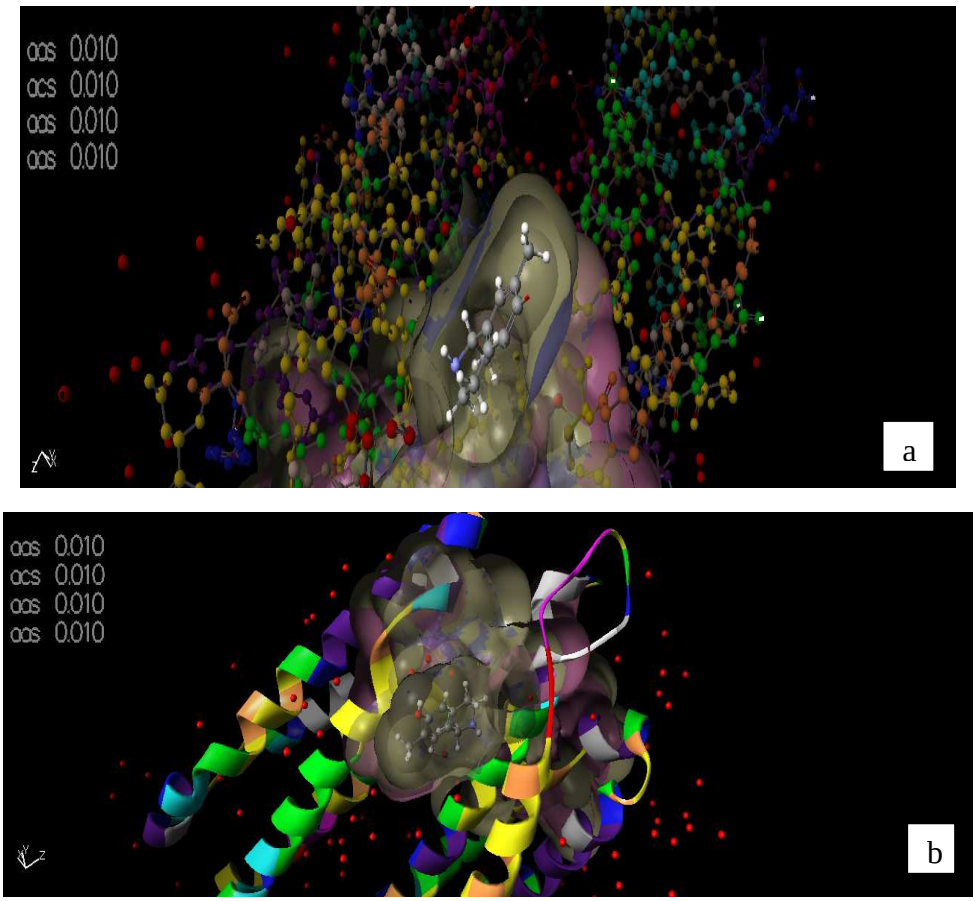


Fig. 5. The molecule of dihydroquercetin in the active site of PDB protein with code 2I9T (the active site in the form of a sphere): a – representation of the protein in the form of molecules; b – representation of the protein in the form of ribbons

RESULTS AND DISCUSSION

As a result of docking a number of values of Consensus scoring functions has been obtained. These values assess the quality and energy of binding of the structures studied (phytosterols, vitamins, flavonoids, saikosaponins, acids, polysaccharides, monoterpenoids, alcohols**)** with the molecules of two biotargets (PDB codes 1VKX, 2I9T). The Consensus function allows to create a rating of compounds and analyze the data regarding the choice of potential agonists/antagonists of the biological target selected. The values of Consensus scoring functions calculated for all compounds are given in Table 1. The values obtained for the structures of different chemical groups were compared with the values of the known hepatoprotector Silymarin.

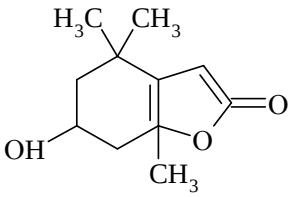
The docking results have proven that affinity of all chemical structures in relation to the NFkB protein (nuclear factor kappa B) (PDB code 1VKX) is insignificant and does not exceed the value for silibinin, which is the main component, and determines the pharmacological activity of hepatoprotector Silymarin (-5.59).

The components in the chemical composition of *Bupleurum aureum* plant have shown a higher level of the affinity calculated in relation to another target studied (PDB code 2I9T). Thus, inhibition of protein (code 2I9T) has been proposed as the most likely mechanism of the hepatoprotective effect.

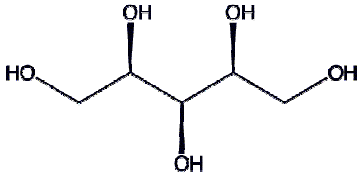
The value of Consensus function allow to make the assumption that for *Bupleurum aureum* plant the hepatoprotective activity may be associated with the presence of flavonoids (quercetin), alcohols (xylitol) and monoterpenoids (lolioside) in its composition.

Table 1. The results obtained while conducting the molecular docking

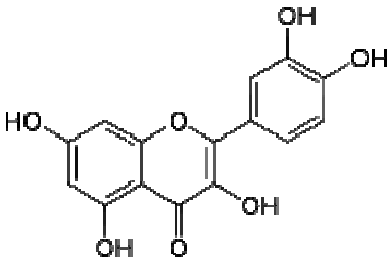
	Consensus docking score	
	Crystallographic models of proteins	
Compounds	1VKX	2I9T
Phytosterols		
Campesterol	-2.01	-27.48
Stigmasterol	-1.73	-4.74
ß-sitosterol	-1.79	-5.459
Spinasterol	-1.70	-3.050
Vitamins		
Rutin	-3.26	-17.950
Ascorbic acid	-2.55	-19.123
Flavonoids		
Quercetin	-2.68	-35.050
Isorhamnetin	-2.34	-13.684
Isoquercetin	-2.26	-12.667
Narcissine	-2.18	-11.012
Saikosaponins		
Saikosaponin A	-1.752	-1.013
Saikosaponin C	-1.665	-1.612
Saikosaponin D	-1.478	-1.795
Acids		
Lauric acid	-1.202	-27.408
Linolenic acid	-1.292	-22.474
Linoleic acid	-1.112	-9.533
Palmitic acid	-1.725	-14.974
Pentadecanoic acid	-1.882	-14.565
Myristic acid	-1.446	-20.254
Gallic acid	-1.332	-7.503
Polysaccharides		
Inulin	-1.564	-2.654
Alcohols		
Xylitol	-3.004	-37.870
Phytol	-2.610	-20.817
Monoterpenoids		
Lolioside	-2.094	-28.004



lolioside



xylitol



quercetin

In comparison with other groups flavonoids, alcohols, monoterpenoids are characterized by a high level of the affinity calculated in relation to the target studied, and, probably, their presence affects the hepatoprotective activity of the plant (Table 1).

CONCLUSION

1 The molecular docking has been conducted for all chemical structures in the composition of *Bupleurum aureum* plant in relation to hepatoprotective biotargets using the “Dock into active site” function.

2. As a result of docking a number of values of Consensus scoring functions has been obtained; it allows to provide affinity of all chemical structures in the composition of *Bupleurum aureum* plant in relation to hepatoprotective targets and identify the structures (quercetin, xylitol, lolioside); their presence affects the hepatoprotective activity of the plant.

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