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Molecular Docking Studies Between Anthraquinone Aloe Emodin and Dengue Virus Protein (Denv-2)

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Abstract- **The dengue fever is a major public health problem because it hits countless countries and about $ 12 billion is spent on mosquito control and treatment. This disease is caused by the Aedes aegypti mosquito and also by the Aedes albopictus, where the virus presents four series of serotypes (DENV-1, DENV-2, DENV-3 and DENV-4), so the individual can contract dengue up to four times throughout his life. The chosen binder was Aloe-emodin, which belongs to the anthraquinone family and can be found in the sap or leaves of Aloe vera. This drug has potent laxative action, antitumor activity, estrogenic activity, consequently, it is a possible potential candidate to be the binder that is able to inhibit the dengue virus. The study was carried out using the dengue virus protein (DENV-2) with the Aloe-emodin ligand, where the molecular docking was performed with the objective of identifying and characterizing a possible interaction between the target protein and the ligand. After the docking, ten attractive twists were obtained, whose torsion # 1.5 had the lowest binding distance of 1,380 Å, between the Hydrogen atom (H23) and the amino acid LEU 351.AH, where this conformation is the most probable and more stable.**

Keywords - Aloe-emodin. Dengue Fever. Docking molecular, theoretical chemistry .

I. INTRODUCTION

Dengue fever is a disease caused by an arbovirus, which belongs to the family Flaviridae and to the genus Flavivirus, being transmitted through the bite of the mosquito Aedes aegypti, remembering that Aedes albopictus has similar proliferative capacity and morphology, where it is responsible for some outbreaks of the disease in Asia. Tropical countries are the most affected by their environmental, climatic and social characteristics [1].This virus presents four serotypes (DENV-1, DENV-2, DENV-3 and DENV-4), where the coexistence of these serotypes can occur in the same region. This is the arbovirose that has the highest occurrence in humans worldwide [2], causing great urban epidemics, which makes it a major public health problem in many developing countries, including Brazil [3]. The main clinical forms of dengue fever are classical dengue fever (Dengue fever), dengue fever with complications (DHF), dengue hemorrhagic fever (DHF) and the most serious of all, which is dengue shock syndrome (SCD) so an individual can acquire this virus up to four times throughout life [4]. Aloe-emodin is a hydroxyanthraquinone and belongs to the anthraquinone family, which can be found in the sap or leaves of *Aloe vera*. The aloe-emodin has a potent laxative action, where it induces chloride secretion in the colonic mucosa and liberates the acetylcholine, which causes in the stimulation of the contraction of the intestinal smooth muscle [5]. It also demonstrates antitumor activity (ED 50 s = 1-13 μM), inducing apoptosis in several cancer cells, increasing the production of reactive oxygen species [6]. Aloe-emodin is reported to have estrogenic activity as a phytoestrogen and has been shown to inhibit the proliferation of breast cancer cells by downregulation of ERα protein levels and thus repressing the transcriptional activation of the receptor [7]. Proteins are organic molecules of high molecular weight, responsible for most of the essential activities of organisms, being constituted in polymers formed by the covalent bond between different amino acids, where the biological activity depends on its structure

[8]. Through molecular modeling, more focused research can be carried out towards the discovery of new biologically active compounds, as well as the optimization of prototypes, inhibitors, enzymatic activators and other ligands that allow the production of more efficient and specific drugs through the development rational use of drugs [9].

Until the mid-1990s, Southeast Asia was the region most affected by dengue [10]. Since then, the countries of Central and South America have started to stand out in this scenario and have contributed to more than half of the reported cases of this disease in the world. In that decade, in just one single year (1998), Brazil registered more than 700 thousand cases [11]. A specific and very current example is the aforementioned epidemic of the municipality of Rio de Janeiro in 2008, which affected other cities in that state, where more than 240,000 cases of FD were reported (1,527 / 100,000 inhabitants), more than 11,000 hospitalizations, 1,364 cases of FHD, 169 confirmed deaths and more than 150 are being investigated [11]. Nearly half of the cases of DHF occurred in the age group under fifteen years of age and the risk of dying was five times greater in children [10]. The southern region of Brazil has the lowest rates of dengue cases, and the states of Rio Grande do Sul and Santa Catarina are considered states without the autochthonous transmission of the disease [12].

From the molecular docking, different spatial conformations of the ligand are obtained, allowing the analyst to identify which of these is the most probable in the target ligand interaction. From each spatial conformation, free energies of binding (between binder and target) are obtained, where the lowest energy is considered the most probable to justify the conformation of the interaction [13]. The interactions between the drug and proteinaceous target occur through intermolecular forces of the dipole type induced and permanent dipole. Among the dipole permanent dipole forces the most common in these systems are the hydrogen bonds, the dipole dipole induced may be forces of Van Der Waals or London [14].

From these computational resources, the cost for the study is much lower when compared to laboratory costs to synthesize and pharmacologically produce various substances. The present study aimed to identify and characterize a possible interaction between dengue virus protein (DENV2) and Aloe-emodin molecule, in order to obtain the attractive kinks for the ligand, the lowest binding distance between the site-receptor and aloe-emodin and which atoms were involved in this interaction.

II. METHODOLOGY

The first step of the work was to obtain the structure and properties of the dengue virus protein (DENV-2), by the Protein Data Bank repository [15-16], whose access code is the 1OAN. Then, we obtained the structure and molecular properties of the drug Aloe emodin, through the Pubchem repository [17], whose access code was 9792. In this work, used a free access software based on the Windows operating system. Protein preparation and molecular docking were performed using the UCSFChimera® software [18].
This software can provide density maps and estimates of the free energy binding between the protein and the ligand, where different spatial conformations of the ligand are obtained, and it is possible for the analyst to identify which of these conformations is most likely in the target binding interaction. The computer used to perform the docking was an intel® Core ™ i3-4150 processor, with 8.00Gb of RAM and a GTX 1050i 4Gb video card.

III. RESULTS AND DISCUSSIONS

Molecular docking is a very efficient method, since it provides several spatial conformations between the protein and the ligand, where for each spatial conformation is obtained binding free energies, so the smaller one with less energy is more likely to justify the conformation of the interaction. Then from the obtained results, it is possible for the analyst to verify which spatial conformation is more feasible for protein-binder binding. To perform molecular docking, this glycoprotein was used (Fig. 1) through the Protein Data Bank repository, where it is registered in the PDB with the access code 1ANAN and its resolution is in the value of 2.75 Â.

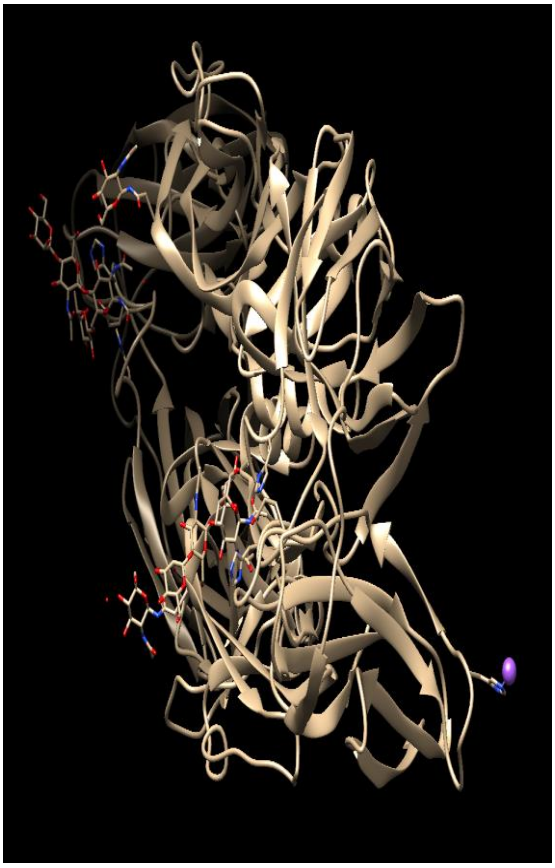

Fig. 1. Structure of dengue virus protein (1OAN).

Source: RCSB Protein Data Bank, 2017.

The second step to perform molecular docking was to obtain the structure and basic molecular properties of the Aloe emodin binder (Fig. 2), where it is known by IUPAC, as: 1,8-dihydroxy-3- (hydroxymethyl) anthracene-9 , 10-dione. This drug has molecular formula C15H10O5 and molecular mass of 270.24 g / mol. Aloe emodin is a hydroxanthraquinone that has laxative, antitumor and estrogenic activity.

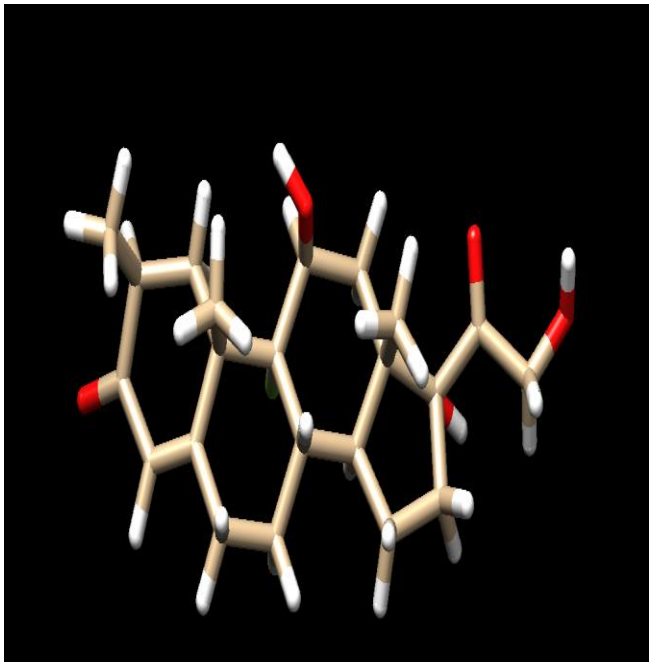

Fig. 2. Molecular structure of Aloe-emodin.
Source: Pubchem Repository.

After the molecular docking between the target protein and its ligand was carried out, ten attractive twists were obtained, where the data were represented in table form.

TABLE I
Attractive twists of docking of the receptor site with aloe-emodin.

Aloe-emodin			
CHIMERA MODEL	SCORE	RMSD L.B	RMSD U.B
#1.1	-5.8	0.0	0.0
#1.2	-5.7	28.478	36.438
#1.3	-5.4	55.482	59.664
#1.4	-5.4	42.712	45.509
#1.5	-5.3	25.483	33.788
#1.6	-5.3	35.142	37.89
#1.7	-5.2	56.438	59.794
#1.8	-5.0	56.215	58.784
#1.9	-4.9	56.335	59.256
#1.10	-4.8	29.575	33.922

After the analysis of the data, we had ten attractive twists between the protein and Aloe emodin, where among the ten, the torsion # 1.5 presented the smallest binding distance in the value of 1,380 Å (Fig. 3),

involving the hydrogen atom (H23) with the amino acid LEU 351.A. Regarding the score function, it was found in the value of -6.9 and for the values of root mean square deviation (RMSD): RMSD lb 2,932 and RMSD ub 3,762 . From Figure 3, it was possible to verify the region with the most probable and stable conformation among all other regions, between the target protein and the ligand.

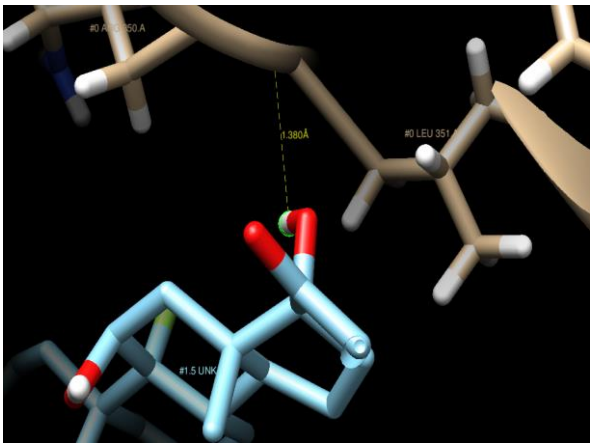

Fig. 3. Molecular docking of the target protein with the aloe-emodin linker.

IV. CONCLUSIONS

Computational chemistry has brought many advances in the field of pharmacology, where thanks to these computational resources it is possible to discover or improve drugs, where this expense is low cost, since when compared to large laboratory expenses to produce and synthesize these substances require a lot of investment and time. In this study, the molecular docking between the dengue virus protein (DENV-2) and the drug Aloe-emodin was performed, obtaining ten attractive twins for this binder, where after the analysis of these twists, we had confirmation that the torsion # 1.5 is the most likely and most stable, due to the fact that it had the shortest bonding distance between the hydrogen atom (H23) and the amino acid LEU 351.AH, valued at 1380 Â °. Then, these results obtained with this study will be used for the revalidation of molecular docking and the molecular dynamics method will be used, in order to know even more this receptor-ligand interaction.

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