Chikungunya Virus Inhibitor Study based on Molecular Docking Experiments

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Abstract: Chikungunya virus disease transmitted by the sting of the mosquito 'Aedes aegypti' presenting an epidemic in some regions. In order to have an early diagnosis and the best treatment technique, it establishes the study of inhibitors for laboratory elaboration of a drug from molecular docking. As a result you have a better chance of using Suramin followed by Silibin.

1 INTRODUCTION

Numerous factors influence the proliferation of the Aedes Aegypti mosquito such as standing water and street litter. This spread of the mosquito is worrisome because it is the cause of numerous diseases such as Dengue and Chikungunya (CHIKV). The current context is very apprehensive, because according to (Weaver et al., 2012). So far there is no antiviral treatment for virus infection and no vaccine licensed to totally inhibit it.

According to (Monath, 2018). There are several clinical and antiviral studies under development to combat Aedes Aegypti transmitted diseases and may provide further specifications for the fight against CHIKV in the future.

The structure used to represent the CHIKV virus was obtained from the work of (Voss et al., 2010), that by X-ray crystallography a model of glycoproteins E1 and E2 represented in 3D format was obtained as shown in the figure. 1 .

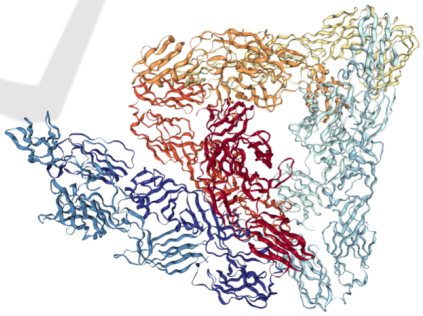

Figure 1: Chikungunya E1 E2 Envelope Glycoproteins.

Therefore, the present work aims to employ computer simulation in different substances in order to present the most efficient inhibitor of Chikungunya virus. The objective of this research is to establish the relationship of the selected molecules with the virus and then to hypothesize new drugs through molecular docking techniques.

Molecular docking is important to predicting the best instruction aiming to adjust a linker to a protein,

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also characterizing the behavior of small molecules in connection with the target proteins. Using this virtual technique, it will be possible to propose structural hypotheses of how ligands are connected to their targets and whether they are possible inhibitors of the virus in question.

In this context, obtaining Chikungunya protein was obtained through the work of (Voss et al., 2010) and ligands through cubichem database.

Research on drugs to inhibit the Chikungunya virus is relevant to both the scientific and social spheres. Since most of the population has had Aedes Aegypti mosquito-related diseases, but so far there is no vaccination or drug that can inhibit the spread of the virus in an individual's body.

The paper is divided into five sections, section 2 deals with possible virus inhibitors, while section 3 emphasizes the computational technique used in the work, Molecular Docking. In section 4 we describe the methodology of the work, in section 5 the results obtained through the simulations and finally the conclusion.

2 CHIKV VIRUS INIBITORS

According to (Monath, 2018) The evolution and spread of the virus is a worldwide concern and the vaccine is the main aspect that can alleviate epidemics. Given this context, there are several options for virus inhibitors to analyze in different ways. In this work Andrographolide, Epigallocatechin gallate, Harringtonine, Silibinin and Suramin were used.Such inhibitors will be classified below.

Andrographolide is a labdane diterpene produced by the plant Andrographis paniculata, which has a wide range of therapeutic applications such as anti-inflammatory and platelet aggregation activities and potential antineoplastic properties. (Gupta et al., 2018) employs Andrographolide as an important bioactive with anti-inflammatory properties, in its work the compounds found in this substance reduce inflammation in various diseases. In research conducted (Gupta et al., 2018),showed the effect of in vitro research of andrographolide in action on the treatment of CHIKV virus, these experiments yielded encouraging results.

Being a compound obtained from green tea, epigallocatechon gallate (EGCG) has inhibitory effects on various viruses. (Weber et al., 2015) described it as an antiviral compound for a variety of viruses, although the exact mechanism of the inhibitory effects are not yet understood, it was included in this research as a candidate for a future drug capable of

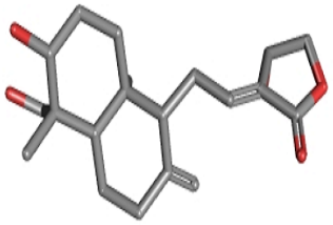

Figure 2: Andrographolide 3D Structure. Source: PubChem. (PubChem, 2005).

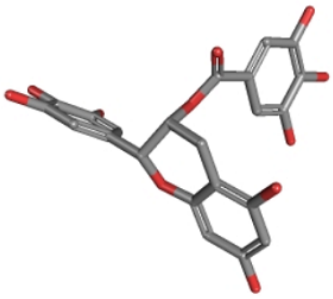

Figure 3: Epigallocatechin gallate 3D structure. Source: PubChem. (PubChem, 2005).

fighting the Chikugunya virus shown in the figure. 3. (Raekiansyah et al., 2018) reported how difficult it is to develop an effective and safe vaccine to combat dengue mosquito-borne diseases. In this work, we investigated the combination of EGCG treatment with suramin drug, this context increased chikungunya inhibition.

Harrigtonine is a substance of the alkaloid family, where they are derived mainly from plants, but may also be derived from fungi, bacteria and even animals. (Kaur et al., 2013) conducted a study on Harringtonine's action in inhibiting CHIK cell replication and subsequently confirmed its effectiveness against the virus. In this study the results indicated that harringtonine acts in the post-initial stage of CHIKV replication and strongly interferes with the viral protein synthesis process. Given this, Harrigtonine is a strong candidate for research on efficient inhibitors of the CHIKV virus. In the figure 6 Harrigtonine molecule in 3D format obtained from the Pubchem database is presented.

A compound of the flavonoid family, silibinin is used to treat a variety of diseases such as hepatitis, liver cirrhosis, and chemical fig-leaf injury. (Lani et al., 2015) carried out research with different flavonoid types among them silibinin, where it presented promising results for CHIVK virus inhibition.

Suramin is a polyanionic compound with an unknown mechanism of action. It is used parenterally in the treatment of African trypanosomiasis and clinical hypotheses have been created to be used as a CHIVK

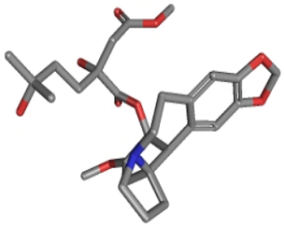

Figure 4: Harringtonine 3D Structure. Source:PubChem. (PubChem, 2005).

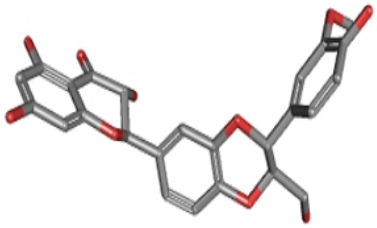

Figure 5: Estrutura 3D Silibinin. Source: PubChem. (PubChem, 2005).

inhibitor. According to (Albulescu et al., 2015) In in vitro experiments suramin proved to be an antiparasitic drug, which obtained satisfactory results in the inhibition and replication of CHIKV and other alphaviruses.

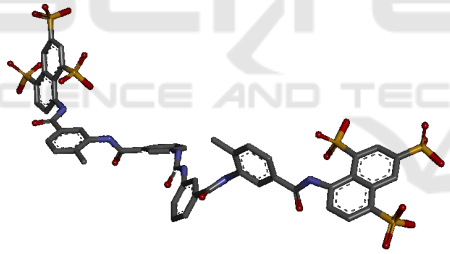

Figure 6: Suramin 3D structure. Source: RCSB PDB. (Berman et al., 2000).

3 MOLECULAR DOCKING

(Ferreira et al., 2015),says molecular docking is a versatile computational technique for the study of biological macromolecules, this technique studies the production of drugs based on molecular structures where they are simulated through numerical interactions by algorithms, where the objective is to predict the bound conformations and binding affinity. between receptor and ligand.

Docking can be defined as a ”key-lock” problem, which has the purpose of predicting the modes of interaction between two molecules knowing only their isolated three-dimensional structures.

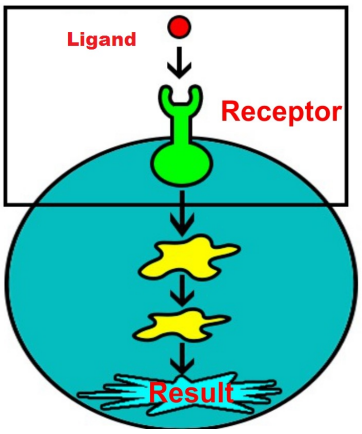

Figure 7: Illustration of the ligand with its receptor molecule.

mode	affinity (kcal/mol)	dist from best mode rmsd l.b.	rmsd u.b.
1	-9.3	0.000	0.000
2	-9.1	120.847	124.985
3	-9.0	121.206	124.330
4	-9.0	2.154	3.997
5	-8.9	76.201	80.717
6	-8.9	53.326	56.975
7	-8.9	52.867	56.820
8	-8.7	0.821	2.025
9	-8.7	53.310	56.939

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Figure 8: Ligand-Receiver Affinity Result Example.

Ligands are molecules produced by cells that interact like a puzzle with its receptor as shown in Figure 7. The receptor, on the other hand, is the target protein in which the interaction between the parts to verify compatibility information is desired.

The practice of this coupling method is for identification and characterization of the binding sites in the target proteins, generating evaluation values of the interaction potential between the target and the ligand. In the figure 8 There is an example of a table showing the results of a simulation performed in autodock vina, which is showing affinity values.

Also according to (Ferreira et al., 2015), The software combines two main components: search algorithm and the score function, in which the algorithm is responsible for searching for possible combinations in the links and the score demonstrates the best binding results obtained during the procedure. The algorithms allow the exploration of various angles, both rotational, translational and conformational of the ligand in the target protein.

In the image 8, a result table is exemplified af-

ter the *molecular dock* on the *software autodock vina*.This table shows the nine best ligand-to-receptor nesting results, where the first column shows the sequence of the numbered results and the second column shows the binding affinity in kcal / mol, representing the highest energy. In the next columns, two variants of RMSD metrics are provided: the rmsd/lb (lower limit of RMSD) an the rmsd/ub (upper limit of RMSD). The rmsd/ub combines each atom in one conformation with itself in the other conformation, ignoring any symmetry, whereas rmsd/lb is defined as follows: rmsd/lb (c1, c2) = max(rmsd'(c1, c2), rmsd'(c2, c1)).

4 METHODOLOGY OF WORK

The methodology has two main objectives: prediction of conformation, and binding affinity.

In the simulations developed in this work the following configurations were used: core i7 fourth generation, 12 GB ram, nvidia p6000 video card, HD Sdd 240 gb.

The molecules presented as ligands in this work were extracted from PubChem, a highly diverse database of molecules maintained by the National Center for Biotechnology Information. The receivers were obtained through the work of (Voss et al., 2010), where the chikungunya virus glycoproteic structure is available in the RCSB PDB Prontein data bank.

The experiment consists in performing the molecular docking simulations using the molecules presented in the section 3, together with the target protein (CHIKV virus). From the results of these experiments, we seek to investigate which ligand had the best protein affinity to stipulate a better candidate for chikungunya inhibitor.

Importantly, before the molecular docking process, the protein goes through a mapping phase of the region where the software must perform the ligand-protein docking simulations. (Vina, 2010) Called this function AutoGrid where you can manually choose the best ligand coupling location, this process will avoid unnecessary processing effort as the region size to try to couple is smaller. As shown 9The entire protein area was used, in which the parameters shown in the image were selected for precise ligand fitting at the best protein site to obtain the best quadrant in common with all ligands.

The coordinates, that is, the parts of the proteins where the ligand will dock, are presented numerically in the image. 10.

To perform the molecular docking process was used autodock vina (performing simulations with receptor and ligands), Mgltools (format conversion of molecules) and PyMol (for visualization of results).

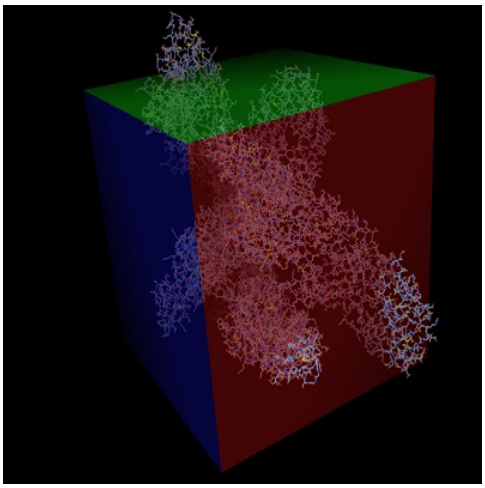

Figure 9: Grid Box Example on Chikungunya Virus Molecule.

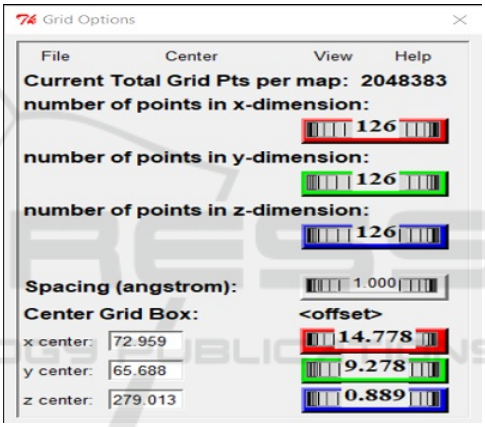

Figure 10: Grid Box Coordinates at Chikungunya Virus Molecule.

5 RESULTS

On the table 1, The best results of molecular docking among ligands are shown. The results that released the most energy (represented by the lowest value results) are the best ligand-receptor fittings. (Shityakov and Förster, 2014) explains that the lower the value presented more significance it will present to the binding found, in which the affinity values in the molecular docking process are favorable only when they are negatively represented. That is, the more negative the value obtained, the better the interaction.

According to table has suramin as a result of lower value. And as a demonstration of your connection you

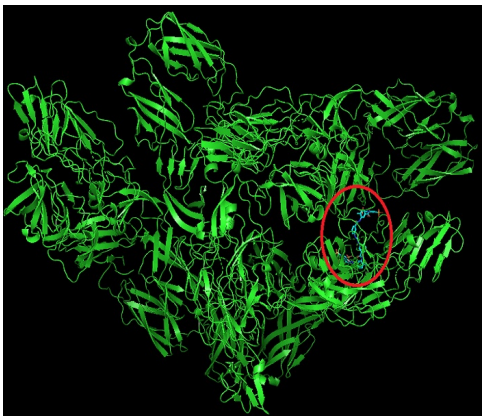

Figure 11: Suramin + Chivk.

Table 1: Affinity Table Of CHUCK Ligands.

	Ligante	Affinity(kcal/mol)
(a)	Andrographolide	-7.9
(b)	Epigallocatechin gallate	-9.1
(c)	Harringtonine	-8.3
(d)	Silibinin	-9.4
(e)	Suramin	-12.7

have the image 11 which represents the Suramin ligand on the protein. In green the main target, the chikungunya virus and in blue the suramin ligand circled in red.

Another interesting factor to note is the quadrant where the active molecules (Andrographolide, Epigallocatechin gallate, Harringtonine, Silibinin and Suramin) had the highest binding value. In the figure 13, the best connecting regions are presented, in which the molecules are coupled, and from these strands can test other possible inhibitors in the quadrant obtained. Since it was observed that in this quadrant the melecules obtained higher binding value. After this phase, one can propose the place where the protein will release the most energy and thus define the guidelines for future inhibitors.

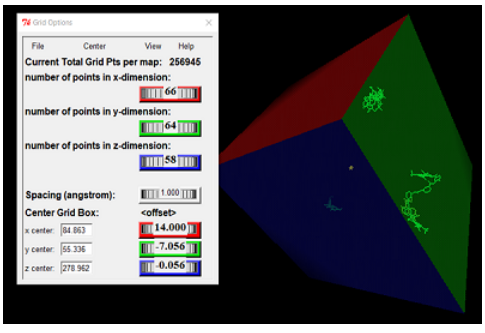

Figure 12: Best Results Coordinates.

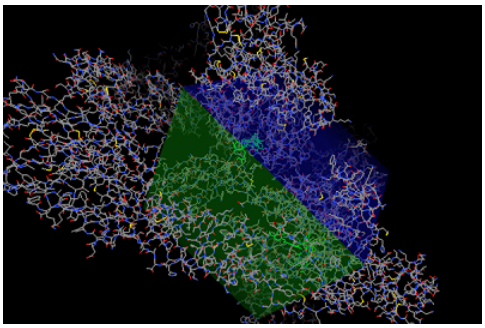

Figure 13: Best ligand Results.

6 CONCLUSION

Computational receptor-ligand docking methodologies are very important tools in the intelligent planning of new drugs. The applied methodology allowed comparing the inhibitors for chikungunya virus through molecular docking techniques, where the inhibitor that obtained the best prediction results of conformation and binding affinity in this simulation was Suramin followed by Silibin.

The conclusion is observed in the values presented in the table 1 que The best result of all ligands was suramin, where it presented -12.7 protein affinity, the binding models obtained are divided into files for multimodal visualization in three-dimensional format to observe where it best fit the protein.

As a continuation of this work consists in in vitro simulations of the combination of these inhibitors with other substances. It can also, as a suggestion of future work, consider the use of other ligands in the coordinates presented in this work, to verify an optimization.

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REFERENCES

Albulescu, I. C., Van Hoolwerff, M., Wolters, L. A., Bottaro, E., Nastruzzi, C., Yang, S. C., Tsay, S.-C., Hwu, J. R., Snijder, E. J., and Van Hemert, M. J. (2015). Suramin inhibits chikungunya virus replica-

tion through multiple mechanisms. *Antiviral research*, 121:39–46.

Berman, H. M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T. N., Weissig, H., Shindyalov, I. N., and Bourne, P. E. (2000). The protein data bank. *Nucleic acids research*, 28(1):235–242.

Ferreira, L., dos Santos, R., Oliva, G., and Andricopulo, A. (2015). Molecular docking and structure-based drug design strategies. *Molecules*, 20(7):13384–13421.

Gupta, S., Mishra, K. P., Dash, P. K., Parida, M., Ganju, L., Singh, S. B., et al. (2018). Andrographolide inhibits chikungunya virus infection by up-regulating host innate immune pathways. *Asian Pacific Journal of Tropical Medicine*, 11(3):214.

Kaur, P., Thiruchelvan, M., Lee, R. C. H., Chen, H., Chen, K. C., Ng, M. L., and Chu, J. J. H. (2013). Inhibition of chikungunya virus replication by harringtonine, a novel antiviral that suppresses viral protein expression. *Antimicrobial agents and chemotherapy*, 57(1):155–167.

Lani, R., Hassandarvish, P., Chiam, C. W., Moghaddam, E., Chu, J. J. H., Rausalu, K., Merits, A., Higgs, S., Vanlandingham, D., Bakar, S. A., et al. (2015). Antiviral activity of silymarin against chikungunya virus. *Scientific reports*, 5:11421.

Monath, T. P. (2018). Chikungunya and zika: The future. In *Chikungunya and Zika Viruses*, pages 367–377. Elsevier.

PubChem (2005). ata deposited in or computed by pubchem. [Online; acesses November 27, 2018].

Raekiansyah, M., Buerano, C. C., Luz, M. A. D., and Morita, K. (2018). Inhibitory effect of the green tea molecule egcg against dengue virus infection. *Archives of virology*, 163(6):1649–1655.

Shityakov, S. and Förster, C. (2014). In silico predictive model to determine vector-mediated transport properties for the blood–brain barrier choline transporter. *Advances and applications in bioinformatics and chemistry: AABC*, 7:23.

Vina, A. (2010). Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading trott, oleg; olson, arthur j. *Journal of Computational Chemistry*, 31(2):455–461.

Voss, J. E., Vaney, M.-C., Duquerroy, S., Vonrhein, C., Girard-Blanc, C., Crublet, E., Thompson, A., Bricogne, G., and Rey, F. A. (2010). Glycoprotein organization of chikungunya virus particles revealed by x-ray crystallography. *Nature*, 468(7324):709.

Weaver, S. C., Osorio, J. E., Livengood, J. A., Chen, R., and Stinchcomb, D. T. (2012). Chikungunya virus and prospects for a vaccine. *Expert review of vaccines*, 11(9):1087–1101.

Weber, C., Sliva, K., von Rhein, C., Kümmerer, B. M., and Schnierle, B. S. (2015). The green tea catechin, epigallocatechin gallate inhibits chikungunya virus infection. *Antiviral research*, 113:1–3.