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# Computation Studies on potential anti-COVID-19 natural compound against The Omicron Variant of SARS-COV-2

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***Abstract*—** For the first time, this short communication aims to carry out the possible antiviral role of a natural compound called Adapalene. This substance has been shown, by the Molecular Simulation method, to be particularly active both in the original SARS-COV-2 protein and in the mutated form Spike protein of SARS-CoV- 2 Omicron (B.1.1.529). The best results obtained have reported excellent Binding Energies Scores values of about -10.35 kcal/mol with an estimated Ki of about 26 nMolar, when Adapalene interacts in the binding active zone of the receptor binding domain (RBD) of SARS-COV-2, with the Human ACE2. Furthermore, this compound can interacts also with other antiviral Coronavirus proteins. Indeed it can bind with other SARS-COV-2 proteins such as SARS-COV-2- 3Cl protease, with an Estimated Binding Energy of approximately, ca -10.24 kcal/mol and an estimated Ki of ca 31.15 nMolar, while with Nucleocapsid Phosphoprotein SARS-COV-2, with a Binding Energy of approximately of ca -10.47kcal / mol and an estimate Ki of ca 21.06 nMolar.

***Keywords***— Covid-19, Adapalene , Docking analysis, SARS-COV-2

## I. INTRODUCTION

COVID-19 disease caused by an infection of the SARS-CoV-2 virus, known as novel coronavirus or 2019-nCoV, was identified in December 2019. and resulted in more than 3,000,000 deaths as of April 25 2021 (WHO https://covid19.who.int/, 2021) [1-4.]

Symptoms of COVID-19 are variable, but frequently include fever, cough, fatigue, breathing difficulties, nausea or vomiting, and loss of smell and taste. The risk of morbidity and mortality from COVID-19 significantly increases in the presence of coexisting medical conditions, while the underlying mechanisms are not yet fully understood [5-9].

COVID-19 is characterized by severe pneumonia and approximately 20% of infected persons develop a severe form of COVID-19, which gives rise to respiratory failure and multiorgan that requires intensive interventions and sub-intensive therapy. Click or tap here to enter text. For these reasons, each government of each Country provides different Recommendations for the Prevention of SARS-CoV-2 It has been shown that this type of virus can cause severe respirators for humans, especially in some by causing extensive alveolar damage [1-9]

Nowadays, it is possible to find a large scientific bibliographical Literature based on the computational study of potential drugs or natural substances, capable of being active against SARS-COV-2 proteins [1-9]. In-silico analysis is often the first approach that is applied before carrying out in Vitro and In Vivo studies. This method, although theoretical, is essential and quite accurate, because it allows in a short time to perform a Virtual Screening Analysis of thousands of potential biological molecules with their relative Binding Energies scores, (in terms of kcal/cal) which, when compared with each other, we can immediately understand which of them can bind very well, in the protein target.

## II. RELATED WORK

Generally speaking, Molecular Docking Tool predicts the preferred orientation of a molecule to a second one when this bind together to form a stable complex. The latter, through well-known various score functions, for instance, Autodock Vina and Autodock 4, allows us to carefully predict and estimate the Binding Energy (kcal mol -1) and the constant inhibition Ki of small molecules in target proteins of interest.

## III. MATERIALS AND METHODS

All proteins were downloaded from Protein Data bank https://www.rcsb.org and they are carefully prepared, and finally, they are saved in PDB format. The first step was the removal of all ligands and crystallized water molecules from crystal proteins, using Chimera software (https://www.cgl.ucsf.edu/chimera/) [10]. Later, Polar Hydrogens and Kollmann charges were added with AutoDockTools, (https://ccsb.scripps.edu/mgltools/downloads/) and they converted to pdbqt format. Regarding Ligand Preparation

 

workflow, Adapalene, Avapritinib, Capmatinib, and Conivaptan were manually downloaded from the PubChem database compound, and they were downloaded from the PubChem Database (https://pubchem.ncbi.nlm.nih.gov/) in 2D SDF format and it is built and minimized by Avogandro program with an FFFF94 force field, with Optimization Algorithm Decrescent and next step, all Hydrogens, and Gasteiger charges were added by Autodock Tools. Final step, they are converted in pdbqt format, before to run Autodock Vina [11] and Autodock 4 [12] docking analysis.

Center Grid Box for AutoDock 4 with Autodock Tools:
-PDB CODE: " 6M0J ACE2 Chain A" X (-25.076) Y 16.035) Z (-25.202 ), Dimension Angstrom X (126) Y(126) Z (126 ), Spacing 0.375 A°, Population Size 150, Run 1-10, Number of Energy evaluations 2500000.
-PDB CODE: 6M0J "Spike S1- ACE2": X (-35.247 ) Y (28.706) Z (5.626 ), Dimension Angstrom X (58) Y(100) Z (62) Spacing 0.375 Population Size 150, Run 1-10, Number of Energy evaluations 2500000.

-PDB CODE: "7T9K SARS-CoV-2 Omicron spike protein Chain A in complex with human ACE2 Chain D" : Center Grid Box Coordinate Grid Box for Autodock4 Docking X (228.428 ) Y (176.668 ) Z (255.432) Dimension Angstrom X (64) Y(114) Z (78) Population Size 150, Run 1-10, Number of Energy evaluations 2500000

-PDB CODE: " 6XQS SARS-CoV-2 Crystal structure of SARS-CoV-2 main protease Chain A : X (9.571 ) Y (1.853 ) Z (24.155) Dimension Angstrom X (40) Y(44) Z (40) Population Size 150, Run 1-10, Number of Energy evaluations 2500000.

-PDB CODE: "6YUN Crystal Structure of C-terminal Dimerization Domain of Nucleocapsid Phosphoprotein SARS COV-2 Chain A" : X (-14.464 ) Y (-2.765 ) Z 18.908) Dimension Angstrom X (126) Y(126) Z (126) Population Size 150, Run 1-10, Number of Enery evaluations 2500000
-PDB CODE: "1O86 Crystal Structure of Human Angiotensin Converting Enzyme Chain A" : Center X (40.783 ) Y (33.185 ) Z 46.986) Dimension Angstrom X (40) Y(44) Z (40), Population Size 150, Run 1-10, Number of Energy evaluations 2500000.

## IV. Results and Discussion

In figure 1, we present the X-ray structure of human testicular ACE and its complex with one of the most widely used inhibitors lisinopril. From our analysis, this drug has shown a Binding Energy of approx -8.0 kcal/mol with Estimated Inhibition Constant Ki of about 871.91 nMolar and also demonstrated to establish several hydrogen bonds and hydrophobic bonds with this receptor protein.) . The next step was to measure the Binding Energy value of our best-proposed substance, in Angiotensin-converting enzyme (ACE), that is Adapalene to be able to make preliminary comparisons of energy estimates. From the docking method, Adapalene reports a comparable value to the drug Lisinopril of approximately -8.27 kcal/mol with Estimated Inhibition Constant Ki of about 1.93 uMolar

From Molecular Docking Investigation, we discovered that among the other drugs we studied, Avapritinib showed a significantly higher binding capacity than Lisinopril, in ACE 2 Angiotensin-converting enzyme 2 protein, with a Binding Energy of approximately -12.00 kcal/mol, as well as Capmatinib with an approximate value of -9.77 kcal. / mol and that of Conivaptan of about -9.79 kcal/mol. The following step of this paper was to focus only on the active area of The receptor binding domain of the SARS-CoV-2 with the area of the Angiotensin-converting enzyme 2 receptors.

In figure 4 and in figure 5 the active areas of Spike protein S1 with Chain E (green color) and ACE-2 with chain A (red color) were reported three-dimensionally. In figure 5, we highlight which amino acids of SARS-COV-2 can bind with those of the ACE2 receptor. The energy values, estimated by the Autodock 4 method, of our 4 best-proposed molecules were then calculated, ie that of Avapritinib (-8.79 kcal/mol), Adapalene (-8.73 kcal/mol), Capmatinib (-8.73kcal / mol) and Conivaptan (-8.18 kcal/mol) As can be seen from these results, none of the 4 reported significant values in energy terms. However, we also have to calculate the scores of the Omicron SARS-CoV-2 Variant Spike Protein

In this case, with great surprise, we not only notice more significant binding values but also that Adapalene can bind well to the viral protein. Indeed, Adapalene has shown a Binding Energy value of ca -10.31 kcal/mol, Avapritinib a Binding Energy value of ca -9.32 kcal/mol, Capmatinib a Binding Energy value of ca -8.03 kcal/mol, and Conivaptan a Binding Energy values of ca -8.20 kcal/mol
In Table 1 , we summarize our important first results comparison drugs Molecular Docking, where we deduce that Adapalene appears to be the most effective with the viral protein. All this allowed us to focus only on Adapalene to understand in detail what its role might be also with the other proteins of SARS-COV-2. The goal of this work is intend to analyze other Coronavirus proteins , for instance SARS-COV-2 3L protease ( $3Cl^{pro}$), essential for its replication within the host cell andf the nucleocapsid SARS-COV--2 protein. In Table 2 we report the comparison of Binding Energies scores after Moleculer Docking analysis.

**Discussion**
We report in Table 2, the main results of Molecular Docking regarding our best proposal medical compound against COVID-19. It is a topical retinoid, named Adapalene is used in the treatment of acne, and it showed exceptional values both in terms of Binding Energy and in estimated Inhibition Constant (Ki) of the order of nanoMolar. This leads us to think that the molecule in question could interact with the Coronavirus, even if

 

further investigative analyzes are needed to understand precisely what is the mechanism of action of adapalene with the Coronavirus.

Table 1. Comparison docking results of Adapalene, Avapritinib Capmatinib, Conivapatan respectively, estimated by Autodock 4 with Autodock Tool.

| **Compounds** | **Molecular Docking by Autodock 4 Algorithm** | | |
|---|---|---|---|
| | ***Estimation of Ki ( constant inhibition)*** | ***Ligand efficiency ( kcal/moL)*** | ***Binding Energies (kcal/mol)*** |
| Docked Adapalene (PDB 6M0J) ACE2 Chain E) | ***310.15 nM*** | ***-0.29*** | ***-8.67*** |
| Docked Avapritinib (PDB 6M0J ACE2 Chain E) | ***1.59 nM*** | ***-0.32*** | ***-12.00*** |
| Docked Capmatinib (PDB 6M0J ACE2 Chain E) | ***68.74*** | ***-0.32*** | ***-9.77*** |
| Docked Conivaptan (PDB 6M0J ACE2 Chain E) | ***67.04 nM*** | ***-0.26*** | ***-9.79*** |
| Docked Adapalene (PDB 6M0J Spike S1-ACE2) | ***396.23*** | ***-0.28*** | ***-8.73*** |
| Docked Avapritinib (PDB 6M0J Spike S1-ACE2) | ***359.2 nM*** | ***-0.24*** | ***-8.79*** |
| Docked Capmatinib (PDB 6M0J Spike S1-ACE2) | ***557.52 nM*** | ***-0.28*** | ***-8.19*** |
| Docked Conivaptan ( 6M0J Spike S1-ACE2) | ***997.8 nM*** | ***-0.22*** | ***310.15 nM*** |
| Docked Adapalene (PDB 7T9K SARS-CoV-2 Omicron spike protein Chain A in complex with human ACE2 Chain D) | ***25.98 nM*** | ***-0.33*** | ***-10.53*** |
| Docked Avapritinib (PDB 7T9K SARS-CoV-2 Omicron spike protein Chain A in complex with human ACE2 Chain D) | ***147.97 nM*** | ***-0.25*** | ***-9.32*** |
| Docked Adapalene (PDB 6M0J) ACE2 Chain E) | ***310.15 nM*** | ***-0.29*** | ***-8.67*** |
| ACE2 Chain D) | | | |
| Docked Capmatinib (PDB 7T9K SARS-CoV-2 Omicron spike protein Chain A in complex with human ACE2 Chain D) | ***1.3 uM*** | ***-0.26*** | ***-8.03*** |
| ocked Conivaptan (PDB 7T9K SARS-CoV-2 Omicron spike protein Chain A in complex with human ACE2 Chain D) | ***978.58 nM*** | ***-0.22*** | ***-8.20*** |

Table 2. Comparison docking results of Adapalene, in complex SARS-COV-2 proteins, estimated by Autodock 4 with Autodock Tool.

| **Compounds** | **Molecular Docking by Autodock 4 Algorithm** | | |
|---|---|---|---|
| | ***Estimation of Ki ( constant inhibition)*** | ***Ligand efficiency ( kcal/moL)*** | ***Binding Energies (kcal/mol)*** |
| **Docked Adapalene (PDB 6M0J ACE2 Chain E)** | *310.15 nM* | *-0.29* | *-8.67* |
| Docked Adapalene (PDB 1O86 Crystal Structure of Human Angiotensin Converting Enzyme Chain A) | *871.91 nM* | *-0.27* | *-8.27* |
| Docked Adapalene (PDB 6M0J Spike S1-ACE2) | *396.23 nM* | *-0.28* | *-8.73* |
| Docked Adapalene (PDB 7T9K SARS-CoV-2 Omicron spike protein Chain A in complex with human ACE2 Chain D) | ***25.98 nM*** | ***-0.33*** | ***-10.35*** |

 

| | | | |
|---|---|---|---|
| Docked Adapalene (PDB 6XQS 3C-like proteinase Chain A) | *396.23* | *-0.28* | *-8.73* |
| Docked Avapritinib (PDB 6M0J Spike S1-ACE2) | ***31.15 nM*** | ***-0.29*** | ***-10.24*** |
| Docked Adapalene (PDB 6YUN Cystal Structure of 6YUN Crystal Structure of C-terminal Dimerization Domain of Nucleocapsid Phosphoprotein SARS COV-2 Chain A) | ***21.06 nM*** | ***-0.34*** | ***-10.47*** |

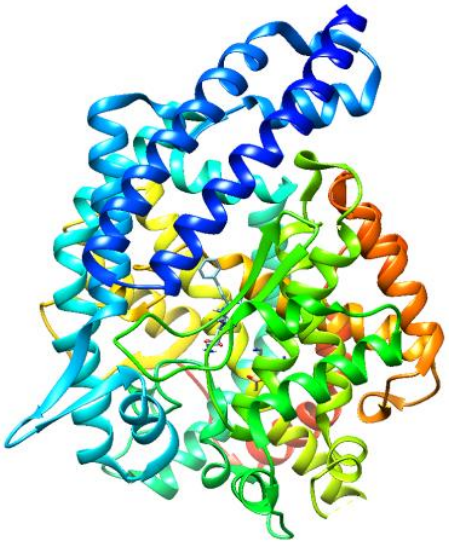

Figure 1. Crystal 3D Structure of Human Angiotensin Converting Enzyme in complex with crystal Lisinopril.

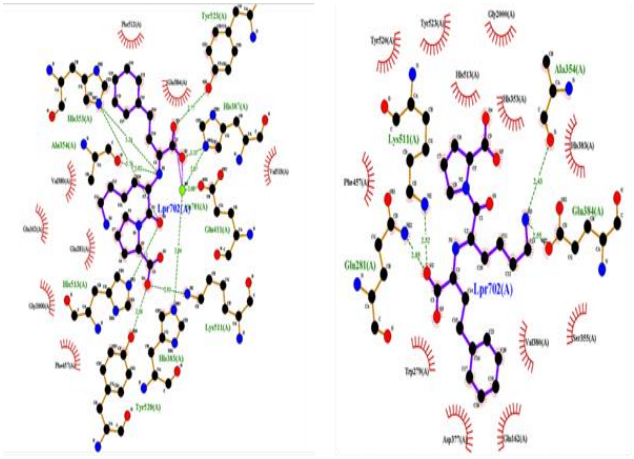

Figure 2. Comparison Crystal and Docked 2D Structure of Human Angiotensin Converting Enzyme in complex with a) crystal and b) Docked Lisinopril with a Binding Energy of ca -8.0 kcal/mol. The figure was reproduced with LIGPLOT program.

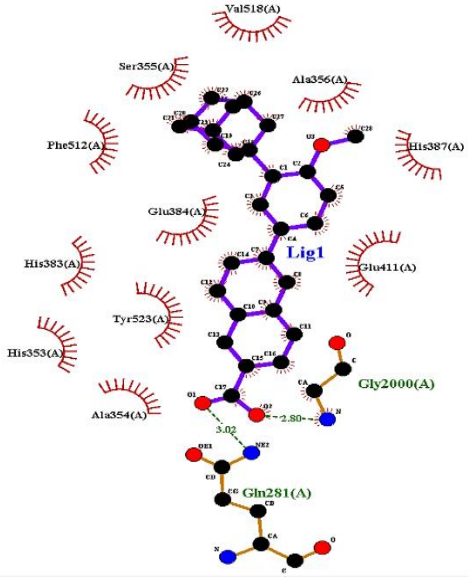


Figure 3. 2D Plot residues interactions bonds of Docked 2D Structure of Human Angiotensin Converting Enzyme in complex with Docked Adapalene with a Binding Energy of ca -827 kcal/mol. The figure was reproduced with LIGPLOT program.

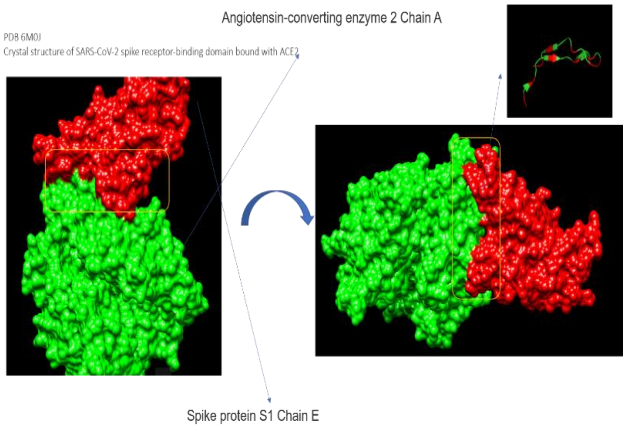


Figure 4. Crystal structure of not changed SARS-CoV-2 spike receptor-binding domain ( green color) bound with ACE2 ( red color) . The figure was reproduced with Chimera software.

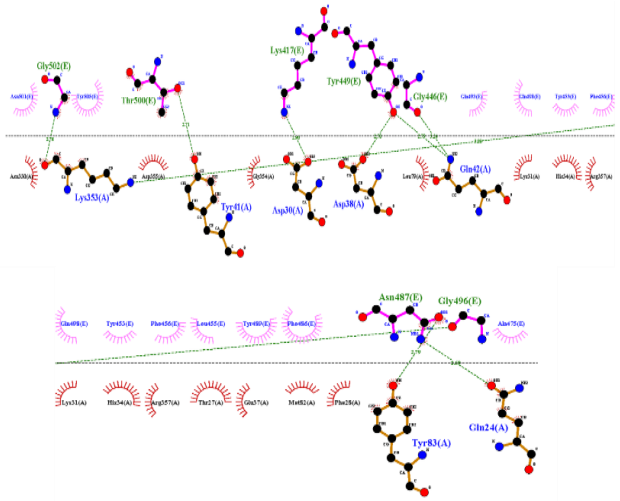


Figure 5. 2D Plot residues interactions bonds in Protein spike receptor-binding domain ( green color) bound with ACE2 ( red color) . The figure was reproduced with Chimera software.

 

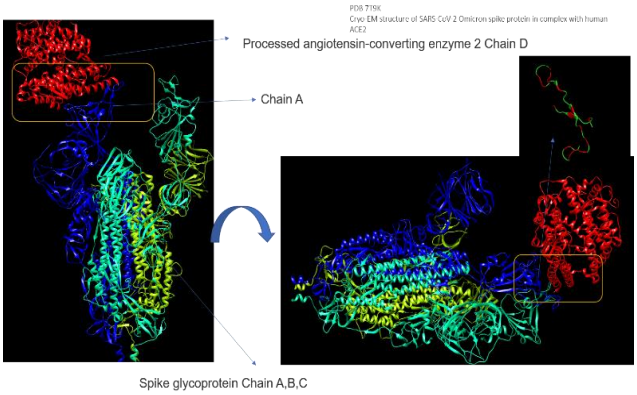


Figure 6. Crystal structure of Omicron SARS-CoV-2 Variant Spike SARS-COV-2 of not changed Crystal structure of SARS-CoV-2 spike receptor-binding domain (pink color) bound with ACE2 ( red color) . The figure was reproduced with LIGPLOT software.

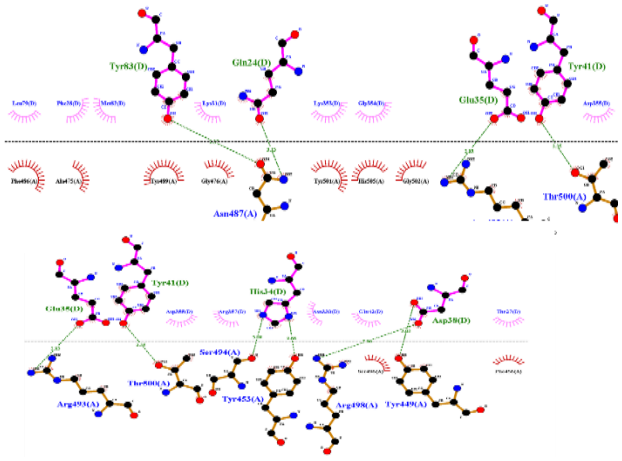


Figure 7. 2D Plot residues interactions bonds of Omicron SARS-CoV-2 Variant Spike Protein spike receptor-binding domain (red color) bound with ACE2 ( pink color) . The figure was reproduced with LIGPLOT software.

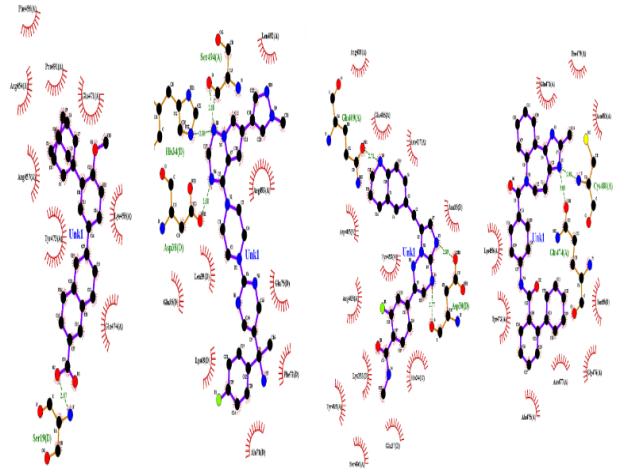

Figure 8. 2D Plot residues interactions bonds of Omicron SARS-CoV-2 Variant Spike Protein spike receptor-binding domain (red color) bound with docked Adapalene ( -10.31 kcal/mol), with Avapritinib ( -10.31 kcal/mol), with Capmatinib ( -8.03 kcal/mol) and with Conivaptan ( -8.20 kcal/mol) respectively. The figure was reproduced with LIGPLOT software.

## V. Conclusion and Future Scope

For the first time, we discovered, by In Silico Approach Analysis, a topical retinoid, called Adapalene, mainly used in the treatment of acne, which it showed to have a potentially active role against SARS-COV-2 proteins. indeed, from docking analysis, it showed exceptional values both in terms of Binding Energy ( kca/mol units) and in estimated Inhibition constant (Ki) of the order of nanoMolar, both Autodock 4 and Autodock Vina Algorithms, even though further investigative analyzes are needed to specifically understand what is the mechanism of action of adapalene with the Coronavirus. Adapalene reported in SARS-CoV-2 Omicron 1- Spike protein a Binding Energy value of -10.35 kcal/mol in Binding Site of of Spike Glycoprotein Receptor and a Binding Energy score of -10.24 kcal/mol in SARS-COV- 2 Main proteases, used for the viral replication in the human body. These theoretical results could be useful for understanding in detail what the biological role of this natural compound is actually against Coronavirus. In is important to point out that these are theoretical preliminary results and further data are needed to better understand the function of Adapalene. Furthermore, only in vitro and in vivo studies can confirm our docking results.

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**Conflict of Interest**
Authors declare that they do not have any conflict of interest.

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