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A Molecular Docking Study of Lopinavir towards SARS-COV-2 Target Protein

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Abstract

COVID-19 was the trigger for the pandemic triggered by SARS-CoV-2. Potential treatments are being used to treat it but there is no specific drug for it. In order to get a particular drug, several drug design techniques are used, in which molecular docking plays a critical role in computer-assisted drug design. In this study, the Lopinavir (LV) molecular docking of the SARS-CoV-2 receptor binding spike proteins was tested. Absorption, distribution, metabolism, excretion and toxicity (ADMET) properties were developed consistent with the expected ADMET parameters provided by Lipinski's rule using Datawarrior software version 5.2.1.

Keywords: SARS-CoV-2, COVID-19, Spike protein, Molecular Docking, Lopinavir.
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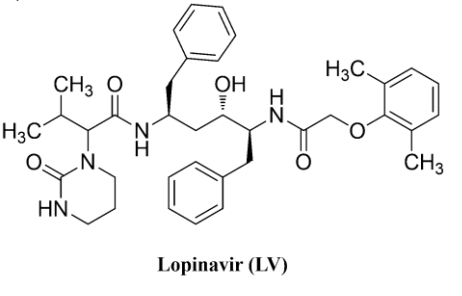
1. Introduction

COVID-19 is caused by the β coronavirus type described in the case of pneumonia of unknown origin found in Wuhan, China.[1] The World Health Organisation (W.H.O.) officially adopted its nomenclature as SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona Virus 2). The SARS-CoV-2 outbreak of coronavirus disease 2019 (COVID-19) poses a significant challenge to global public health.[2] On 30 January 2020, COVID-19 was formally declared a public health emergency of international significance by the WHO.[3] WHO status survey dated 29 May 2020 specifies that there are 5 701 337 reported cases of 357 688 deaths worldwide.[4] The research-based pharmaceutical industry is working on new pharmaceutical chemistry techniques in which molecular simulation is a powerful method for the Structure-Activity Relationship (SAR) study.[5] Molecular docking is one of the most sophisticated methods used in the Structure Based Drug Design (SBDD) due to its ability to expect, with a high degree of precision, the conformation of small molecular ligands inside the appropriate target binding site.[6] A important advancement in drug exploration is the development of molecular docking as a major means of drug discovery today.[7] Molecular docking algorithms provide results for quantitative energy binding markers, including a variety of docked compounds backed by the binding affinity of ligand receptor complexes with pharmacokinetic properties (ADMET: absorption, distribution, metabolism, excretion and toxicity).[7-9] Lopinavir (LV) is a drug approved by the FDA that serves as a protease inhibitor and is commonly used in the treatment of HIV patients.[10] Lopinavir/ritonavir combination is used as a second line of protection in the treatment of HIV as recommended by W.H.O..[11] Ritonavir aims to suppress the metabolic enzyme P450 3A and therefore improves the half-life of Lopinavir.[12] As LV is a protease inhibitor that inhibits the action of the enzyme needed by the Human Immuno Deficiency Virus, it may be helpful in the treatment of COVID-19. There is evidence that Lopinavir/ritonavir is selective against some other coronavirus.[13] To make the above topic clear, we docked Lopinavir with the SAR-COV-2 Spike protein receptor binding as the target. Fig. 1 shows the Lopinavir structure (LV).



Lopinavir (LV)

Fig. 1: Structure of Lopinavir (LV).

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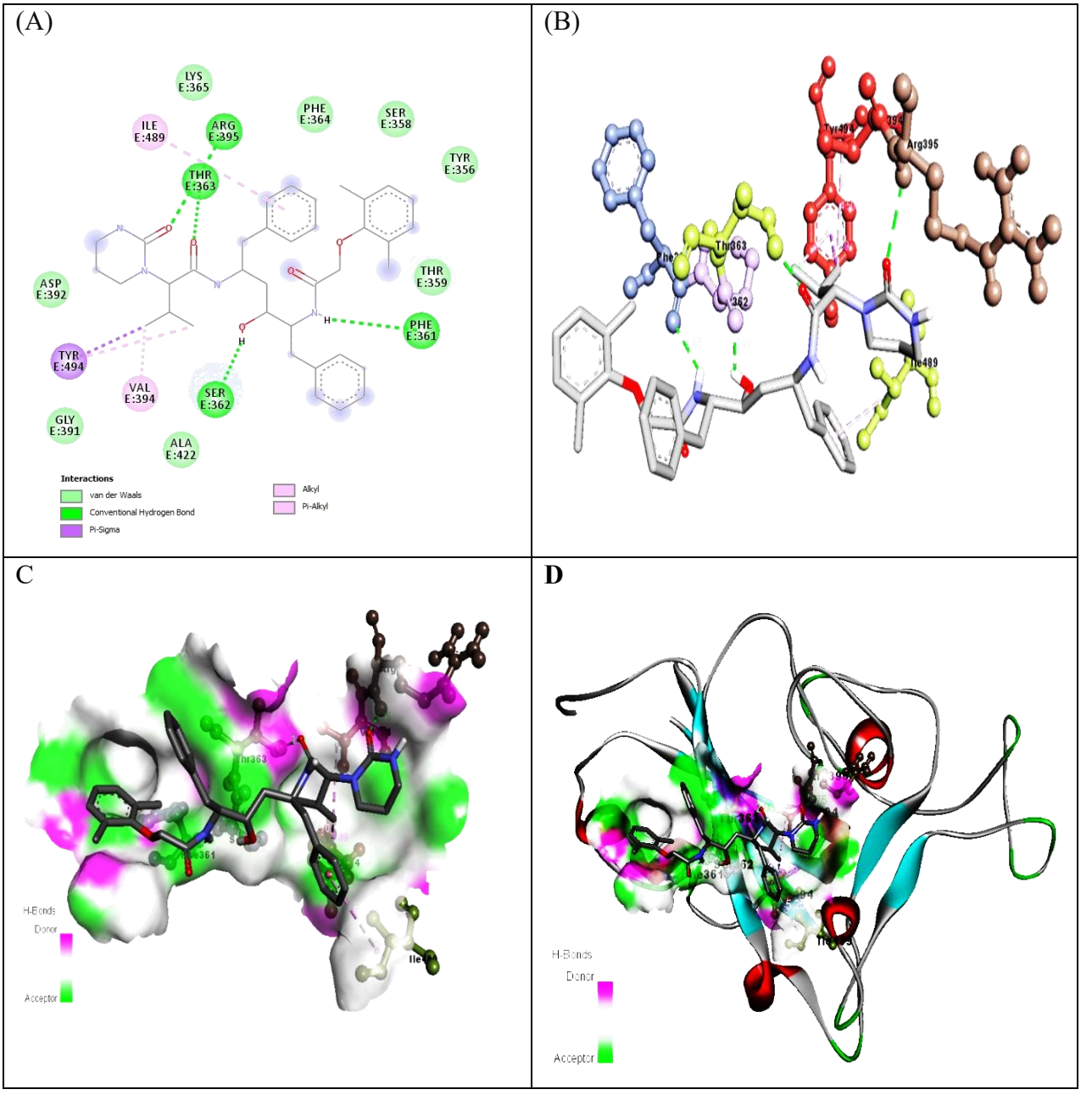


Fig. 2: Conformational changes observed due to the binding of ligand Lopinavir with PDB ID: 2AJF (**A)** is 2D interactions of Lopinavir, (**B)** is 3D interactions formed by the Lopinavir, whereas **(C), and (D)** shows the surface area interactions of Lopinavir with receptor binding domain of SARS-CoV-2.

2. Computational work

2.1 Docking methodology

The practice of molecular docking is useful in yielding valuable information for designing ligands for known active sites of the macromolecules like proteins. For docking analysis, AutoDock 4.2 was employed using the quality protocol mentioned in the literature.[14-16] The X-ray crystal structure of the target protein was retrieved from the RCSB protein data bank.[17] Macromolecule having PDB ID: 2AJF is the structure of the SARS coronavirus spike receptor-binding site, which is complexed with its receptor.[17] We docked Lopinavir with the PDB ID: 2AJF. Also, the property-based approach was achieved using Data warrior the program version 5.2.1 for generating ADMET properties.[18] The spike protein on the receptor binding of SARS-COV-2 was considered because of the target for this docking analysis.

3. Results and discussion

The docking studies of Lopinavir against the SARS-CoV-2 receptor binding site complexed with its receptor (PDB ID: 2AJF) exposed the interaction of Lopinavir with THRE: 363, ARGE: 395, TYRE: 494, PHEE: 361, SERE: 362, VALE: 394, ILEE: 489 are illustrated in Fig. 2A. The negative value of binding energy i.e. (-5.60Kcal/mol) suggests the stability of the complex (Table. 1).

4. Evaluation of binding energy

The strength of a protein-ligand complex is set forth to the intermolecular interactions between these binding partners, solvent effects, and dynamics. So by employing all-atom molecular dynamics (MD) simulations, we are capable to test all of those together. But, to avert different computational costs linked to these simulations, during the molecular docking, the scoring functions were used to grant a rapid and simple evaluation of the binding dynamics of the expected ligand-receptor complexes.[19-20] The docking results of the binding energy of Lopinavir are stated in Table 1. We subdivide the ADMET parameters of Lopinavir as ADME* and Toxicology in Table 2. And Table 3.

Table 1. Docking results for the binding affinity of Lopinavir (LV) with target PDB ID: 2AJF.

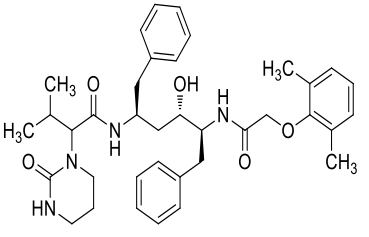
Compound Name	Compound Structure	Binding energy (Kcal/mol)	Predicted IC50 value	Interacting Amino acids
LV		-5.60	78.30 µM (micromolar)	THRE:363, ARGE:395, TYRE:494, PHEE:361, SERE:362, VALE:394, ILEE:489

Table 2. ADME* parameters of the Lopinavir (LV).

Compound code	Molecular Formula	Mol.wt.	Log P	H-bond donors	H-Bond acceptors	Rotatable bonds	TPSA	ADME pass/fail
LV	$C_{37}H_{48}N_4O_5$	628.811	4.847	4	9	15	120	FAIL

Table 3. Toxicology profile for the present studied compounds.

Compound Name	Mutagenic	Tumorigenic	Effect on reproductive system	Eye irritant
LV	NONE	NONE	NONE	HIGH

5. Conclusion

This study aims to identify the potential of Lopinavir (LV) to inhibit COVID-19 by acting on the Receptor Binding Domain of the SARS-CoV-2. The obtained results by molecular docking showed that LV may inhibit COVID-19 giving the same or better energy score as compared to drugs that are under clinical tests. Those results encourage further in *vitro* and in *vivo* investigations of Lopinavir.

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Supporting information

Not applicable

Conflict of interest

There are no conflicts to declare.

References

[1] V. S. Shaikh, G.M. Nazeruddin, S.H. Bloukh, Y.I. Shaikh, Z. Edis, H.M. Pathan, *Engin. Sci.,* 2020, **10**, 11-23 doi: 10.30919/es8d1009.

[2] C. Wu, Y. Liu, Y. Yang, P. Zhang, W. Zhong, Y. Wang, Q. Wang, Y. Xu, M. Li, X. Li, M. Zheng, L. Chen, H. Li, *Acta Pharm. Sin. B*, 2020,10, 766-788, doi: 10.1016/j.apsb.2020.02.008.

[3] W X. Li, W. Wang, X. Zhao, *J.Med. Virol.*, 2020, **92**, 501-511, doi: 10.1002/jmv.25701.

[4] WHO Situation report dated on 29th May 2020. Available on https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200529-covid-19-sitrep-130.pdf?sfvrsn=bf7e7f0c_4.

[5] J. Weigelt, *Exp. Cell Res.*, 2010, **316**, 1332-1338, doi: 10.1016/j.yexcr.2010.02.041.

[6] X.Y. Meng, H.X. Zhang, M. Mezei, M. Cui, *Curr Comput Aided Drug Des.*, 2011, **7**, 146-157, doi: 10.2174/157340911795677602.

[7] F. López-Vallejo, T. Caulfield, K. Martínez-Mayorga, *Comb. Chem. High Through. Scre.*, 2011, **14**, 475-487, doi: 10.2174/13862071179576786.

[8] S. Y. Huang, X. Zou, *Int. J. Mol. Sci.,* 2010, **11,** 3016-3034, doi: 10.3390/ijms11083016.
[9] C. A. Lipinski, F. Lombardo, B.W. Dominy, P.J. Feeney, *Adv. Drug. Deliv. Rev.,* 2001, **46**, 3-26, doi: 10.1016/s0169-409x(00)00129-0.
[10] FDA Approved Drug Products: Kaletra (lopinavir/ritonavir) for oral Use: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021251s058,021906s053lbl.pdf.
[11] Clinton Health Access Initiative. HIV market report, 2019, Available on, https://3cdmh310dov3470e6x160esbwpengine.netdnassl.com/wpcontent/uploads/2019/12/2019-HIV-Market- Report .pdf.
[12] AbbVie. Kaletra Prescribing Information 2020, Available on, www.rxabbvie.com/pdf/kaletratabpi.pdf accessed 03 April 2020.
[13] C.M. Chu, V.C. Cheng, I.F. Hung, *Thorax*, 2004, **59**, 252-6, doi: 10.1136/thorax.2003.012658.
[14] R. Huey, G. M. Morris, A. J. Olson, D. S. Goodsell, *J. Comput. Chem.*, 2007, **28**, 1145-1152, doi: 10.1002/jcc.20634.
[15] G. M. Morris, R. Huey, W. Lindstrom, M. F. Sanner, R. K. Belew, D. S. Goodsell, A. J. Olson, *J. Comput. Chem.*, 2009, **16**, 2785-91, doi: 10.1002/jcc.21256.
[16] G. M. Morris, D. S. Goodsell, R.S. Halliday, R. Huey, W. E Hart, R. K. Belew, and A. J. Olson, *J. Comput. Chem.,* 1998, **19**, 1639-1662.
[17] F. Li, W. Li, M. Farzan, S.C. Harrison, *Science,* 2005, **309**, 1864-1868, doi:10.1126/science.1116480.
[18] T. Sander, J. Freyss, M. von Korff, C. Rufener, *J. Chem. Infor. and Modell.*, 2015, **55**, 460-473, doi: 10.1021/ci500588j.
[19] N. Foloppe, R. Hubbard, *Curr. Med. Chem.,* 2006, **13**, 3583-3608, doi: 10.2174/092986706779026165.
[20] A.N. Jain, *Curr. Protein. Pept. Sci.*, 2006, **7**, 407-420, doi: 10.2174/138920306778559395.

