



## RESEARCH ARTICLE

# Coronavirus disease 2019 drug discovery through molecular docking [version 1; peer review: 1 approved, 2 approved with reservations]

Sweta Singh <sup>1</sup>, Hector Florez <sup>2</sup>

<sup>1</sup>Savitribai Phule Pune University, Pune, India

<sup>2</sup>Universidad Distrital Francisco Jose de Caldas, Bogota, Colombia

**v1** **First published:** 03 Jun 2020, 9:502  
<https://doi.org/10.12688/f1000research.24218.1>  
**Latest published:** 03 Jun 2020, 9:502  
<https://doi.org/10.12688/f1000research.24218.1>

## Abstract

**Background:** The dawn of the year 2020 witnessed the spread of the highly infectious and communicable disease coronavirus disease 2019 (COVID-19) globally since it was first reported in 2019. Severe acute respiratory syndrome coronavirus-2 is the main causative agent. In total, 3,096,626 cases and 217,896 deaths owing to COVID-19 were reported by 30th April, 2020 by the World Health Organization. This means infection and deaths show an exponential growth globally. In order to tackle this pandemic, it is necessary to find possible easily accessible therapeutic agents till an effective vaccine is developed.

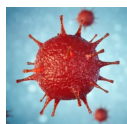
**Methods:** In this study, we present the results of molecular docking processes through high throughput virtual screening to analyze drugs recommended for the treatment of COVID-19.

**Results:** Atovaquone, fexofenadine acetate (Allegra), ethamidindole, baicalin, glycyrrhetic acid, justicidin D, euphol, and curine are few of the lead molecules found after docking 129 known antivirals, antimalarial, antiparasitic drugs and 992 natural products.

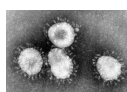
**Conclusions:** These molecules could act as an effective inhibitory drug against COVID-19.

## Keywords

COVID-19, SARS-CoV-2, Molecular Docking



This article is included in the [Disease Outbreaks gateway](#).



This article is included in the [Coronavirus collection](#).

## Open Peer Review

Reviewer Status

	Invited Reviewers		
	1	2	3
<b>version 1</b> 03 Jun 2020	 report	 report	 report

- Elio Rodrigo Castillo**, CONICET-UNaM, Posadas, Argentina
- Fernando Yepes-Calderon** , Children's Hospital Los Angeles, Los Angeles, USA  
SBP LLC, Reserach and Development, Fort Pierce, USA
- Pritha Ghosh** , International Institute of Molecular and Cell Biology in Warsaw, Warsaw, Poland

Any reports and responses or comments on the article can be found at the end of the article.

**Corresponding author:** Hector Florez ([haflorezf@udistrital.edu.co](mailto:haflorezf@udistrital.edu.co))

**Author roles:** **Singh S:** Formal Analysis, Investigation, Validation, Writing – Original Draft Preparation; **Florez H:** Funding Acquisition, Methodology, Supervision, Writing – Review & Editing

**Competing interests:** No competing interests were disclosed.

**Grant information:** This work was supported by the research group Infor-mation Technologies Innovation (ITI) (<https://www.itiid.org/>), which belongs to the Universidad Distrital Francisco Jose de Caldas located in Bogotá Colombia.

*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

**Copyright:** © 2020 Singh S and Florez H. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**How to cite this article:** Singh S and Florez H. **Coronavirus disease 2019 drug discovery through molecular docking [version 1; peer review: 1 approved, 2 approved with reservations]** F1000Research 2020, 9:502 <https://doi.org/10.12688/f1000research.24218.1>

**First published:** 03 Jun 2020, 9:502 <https://doi.org/10.12688/f1000research.24218.1>

## Introduction

Coronavirus Disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), that is responsible for respiratory illness and probably many more is yet to be discovered. This novel virus was first identified on 30<sup>th</sup> December, 2019, with its first infection case infecting a human, which was reported in Wuhan city located in Hubei, China<sup>1</sup>. Coronaviruses are mainly zoonotic, and are present amongst birds and mammals, causing respiratory, neurological, hepatic and enteric diseases<sup>2</sup> as well as comprises of enveloped RNA. The World Health Organization (WHO) declared this disease as a pandemic on 11th March, 2020 and SARS-CoV-2 as the deadliest virus till date on earth claiming 217,896 deaths till 30<sup>th</sup> April, 2020<sup>3</sup>.

Then, it is necessary for the rapid development and approval of a vaccine, which is not yet available<sup>4</sup>. Nevertheless, Chang *et al.*,<sup>5</sup> have suggested that some drugs against same type of viruses approved by the US Food and Drug Administration (FDA) might offer promising results. Hydroxychloroquine is one such drug that is used worldwide whereas Remdesivir and Ivermectin have been reported to work against COVID-19 *in silico* by others.

The transmission of this coronavirus occurs due to the binding of the CoV spike protein to the angiotensin converting enzyme 2 (ACE2) receptor present on the cell surface of the human host. The ACE2 receptor is present in the respiratory organs, kidneys, gastrointestinal tract (at high levels in the esophagus, colon, and small intestine, but low in the stomach), and testes. Virulence of this novel virus is due to the presence of main protease responsible for virus replication along with many major functions<sup>6</sup>. Therefore, we have employed the main protease structure 6m03 as the target protein to identify the best inhibitory drugs *in silico* for our study.

SARS-CoV-2 (negatively stained) when observed under the electron micrograph was found to be spherical in shape with some pleiomorphic characteristic. The epithelial sections of human airway when observed, viruses were found in membrane bound vesicles in cytoplasm along with inclusion bodies. The virions appear similar to solar corona due to 9- to 12-nm distinctive spikes and the virions are 60 to 140 nm in diameter. Thus, it was established due to these morphological characteristics that this virus belongs to the Coronaviridae family along with its genome having more than 85% identity with a bat SARS-like CoV (bat-SL-CoVZC45, MG772933.1) genome as previously assessed via genome sequencing<sup>6</sup>. SARS-Cov-2 initially infects lower airways, binds to ACE2 receptor on cells activating immune cells, thus, inducing the secretion of inflammatory cytokines and chemokines in human pulmonary system<sup>4</sup>. Most COVID-19 patients exhibit flu-like symptoms within a span of two weeks from the exposure to the virus whereas there have been a majority rise in the asymptomatic COVID-19 patients.

In this work, we have performed high throughput virtual screening since it is the fastest approach in finding the probable drug against the target. High-throughput virtual screening

(HTVS) of two databases was carried out via PyRx (Python prescription) software, which uses dock, Vina and Autodock as the docking tool. Autodock itself uses MGLTools comprising of computer aided drug discovery (CADD) pipeline for high throughput virtual screening of large databases for probable hits as target drugs. HTVS enables docking of multiple ligands on a single protein. PyRx is a freely available HTVS software. Docking results are based on the identification of pose visually and quantitatively using a scoring algorithm. Docking calculates the free binding energy ( $\Delta G$ ) between the ligands and the protein. The free binding energy, thus calculated, is fundamental to the formation of complex systems in biochemistry and molecular biology. Lower free binding energy corresponds to a more favorable ligand binding affinity between a receptor and a ligand<sup>7</sup>.

## Methods

### Molecular docking

Molecular docking is a bioinformatics method that allows predicting the orientation of a molecule, when it is bounded to another molecule<sup>8,9</sup>. There are two main approaches for molecular docking. The first approach describes the protein and the ligand as complementary surfaces<sup>10</sup>. The second approach simulates the docking process calculating the ligand protein interaction based on the free binding energy  $\Delta G$ <sup>11</sup>.

### Molecule selection

Selection of database and the COVID-19 main protease structure In this study, we have docked the X-ray crystal structure of main COVID protease protein (PDB ID: 6M03, resolution: 2 Å) with 129 molecules obtained from DrugBank and 992 molecules from the Zinc Natural Product database. The list of 129 molecules are provided along with the link for Zinc natural database in the *Extended data*<sup>12</sup>. These 129 molecules chosen were either antimalarial, antiparasitic, antibiotics, or antivirals, since hydroxychloroquine, remdesivir and ivermectin are antimalarial, antiviral and antiparasitic drugs, respectively. The Zinc Natural Product Database was chosen since most of the drugs are natural derivatives used against various diseases at present and it is a freely available database. Similarity search could not be undertaken since there is no known drug to function 100% against this novel disease at time of publication.

### Processing of macromolecules and ligands

Docking requires processing of the macromolecules and the ligands<sup>13,14</sup>. Water molecules were removed, polar hydrogen bonds were inserted into the crystal structure of 6m03 and it was converted to PDBQT format using AutoDock version 4. The energy of all ligands were minimized and they were converted into PDBQT files using Open Babel version 2.2.3 in PyRX version 0.8<sup>15</sup>.

### Molecular docking process

The grid box was determined as center the coordinates X:12.2632, Y:12.3998, and Z:5.4737, while as dimension the coordinates X:29.9242, Y:64.1097, and Z:48.1126.

The docking was done using Vina version 2.0 in PyRX. After the run, the out files stored in the user folder where the path run

was specified in the edit preference. These output files were stored in PDBQT files, each having nine poses. The autodock application file was launched which then showed the empty dashboard along with “File” on the left hand corner of the page. The out file models were loaded using the “read molecule” application from the selected out file folder. Different poses were analyzed in the AutoDock tool. The pose with the lowest binding energy in kcal/mol was selected for further analysis. The docked molecules were then further converted into PDB format in PyMol and their interaction was studied using the software Discovery Studio version 4.1. The interaction can also be studied with PyMol but a better quality picture is obtained via Discovery studio. Three known drugs (hydroxychloroquine, remdesivir and ivermectin) were first docked against the virus main protease to check their binding energy. The interaction of these three drugs with the COVID-19 main protease could later be utilised for getting the hits.

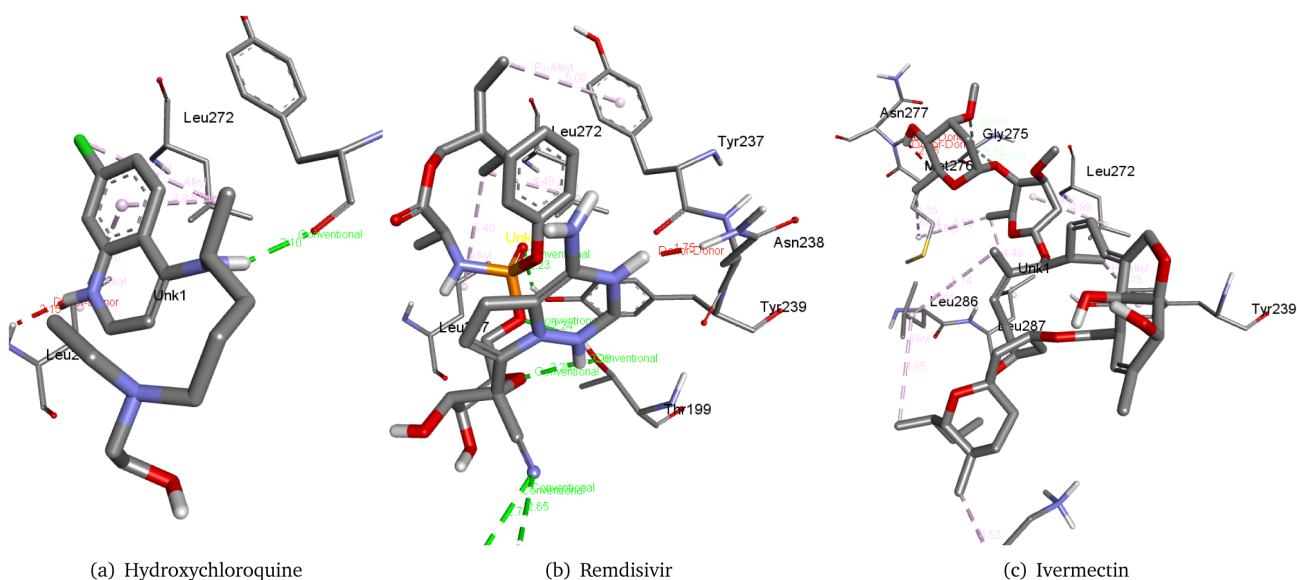
## Results

### Docking results for reference molecules

The free binding energy for drugs known to act against COVID-19, which are hydroxychloroquine, remdesivir, and ivermectin, were found to be -5.5 kcal/mol, -6.3 kcal/mol, and -8.7 kcal/mol respectively as indicated in Table 1, which describes:

**Table 1. Docking of known COVID-19 inhibitors.**

PubChem CID	Drug Name	Binding energy kcal/mol
6321424	Ivermectin	-8.7
121304016	Remdesivir	-6.3
3652	Hydroxychloroquine	-5.5



**Figure 1. Reference molecules hydroxychloroquine, remdesivir, and ivermectin in complex with the COVID-19 main protease 6M03.**

a) PubChem compound ID (CID), which is the compound identifier in the PubChem database from where the 3D mol files of 129 molecules were downloaded; b) common drug name; and c) the free binding energy obtained after docking.

These drugs are known to improve the condition to some extent and yet their functions against COVID-19 are under study<sup>16–19</sup>.

Therefore, we used these three molecules as our reference drugs. The interaction of these drugs with the virus main protease can be seen in the Figure 1. We could observe the interaction of these reference molecules as hydroxychloroquine forms a hydrogen bond with Tyr237 residue of the 6M03 main protease with a distance of 2.10 Å. It also interacts with Leu272 and Leu287. Remdesivir forms six hydrogen bonds with Lys137, Thr199, and Tyr239 along with interacting with Leu272, Leu287, Tyr237, and Asn238 residues of the 6M03 main protease. Ivermectin interacts with Leu272, Tyr239, Leu286, Leu287, Gly275, Asn277, and Met276 residues of the 6M03 main protease.

### Docking results for 129 additional molecules

Keeping the free binding energy of our reference molecules in mind, we shortlisted 77 molecules from the database of 129 molecules with a cut of -6 kcal/mol free binding energy. Eprinomectin, artefenomel, doramectin, betulinic acid, atovaquone, and tetrandrine showed the lowest binding energies, at -9 kcal/mol, -8.7 kcal/mol, -8.4 kcal/mol, -8.4 kcal/mol, -8.2 kcal/mol and -8 kcal/mol, respectively. Table 2 presents the details of the best performing 18 of the 77 molecules along with their CID. These molecules have been considered due to the lowest free binding energy between the ligand and protein. Furthermore, their interactions with the virus main protease 6m03 was studied. Artefenomel interacts with Pro108, Val202, Ile249, Pro293, and Phe294 residues of the 6M03 main

**Table 2. Docking of drugs for probable COVID-19 inhibition.**

	PubChem CID	Drug Name	Binding Energy kcal/mol
1	6450531	Eprinomectin	-9
2	24999143	Artefenomel	-8.7
3	9832750	Doramectin	-8.4
4	64971	Betulinic acid	-8.4
5	74989	Atovaquone	-8.2
6	73078	Tetrandrine	-8
7	6918632	Emodepside	-7.9
8	124081896	Baloxavir marboxil	-7.9
9	122262	Piperaquine	-7.9
10	35802	Flubendazole	-7.8
11	6917864	Artesunate	-7.6
12	40692	Mefloquine	-7.6
13	4030	Mebendazole	-7.6
14	21389	Imidocarb	-7.6
15	9832912	Moxidectin	-7.5
16	439530	Puromycin	-7.5
17	6323491	Radicicol	-7.4
18	54671203	Doxycycline	-7.4
19	107771	Pyronaridine	-7.4
20	11979956	Hachimycin	-7.3

protease. Eprinomectin forms a hydrogen bond (2.26 Å) with Lys5 residue of the 6M03 main protease and also interacts with Leu286, Leu287, and Asn277. Tetrandrine forms a hydrogen bond with Arg131 and also interacts with Leu272, Leu286 and Leu287. Betulinic acid forms a hydrogen bond with Arg137 with 2.66 Å distance and also interacts with Leu272, Leu286, Leu287, Tyr237, and Tyr239. Doramectin forms three hydrogen bonds with Thr199, Lys5, and Gly138 as well as interacts with Leu286 and Asp289. Atovaquone forms a hydrogen bond with the Thr199 residue of the 6M03 main protease with a distance of 2.48 Å and also interacts with Lys137, Leu272, Leu286, Leu287, and Tyr239. These interactions can be observed in [Figure 2](#). Full results are available in the *Extended data*<sup>12</sup>.

### Docking Results for natural molecules

A total of 34 molecules of natural origin were chosen from the datasets of 992 molecules with a cut off -8.9 kcal/mol. [Table 3](#) presents the details of the best 20 molecules along

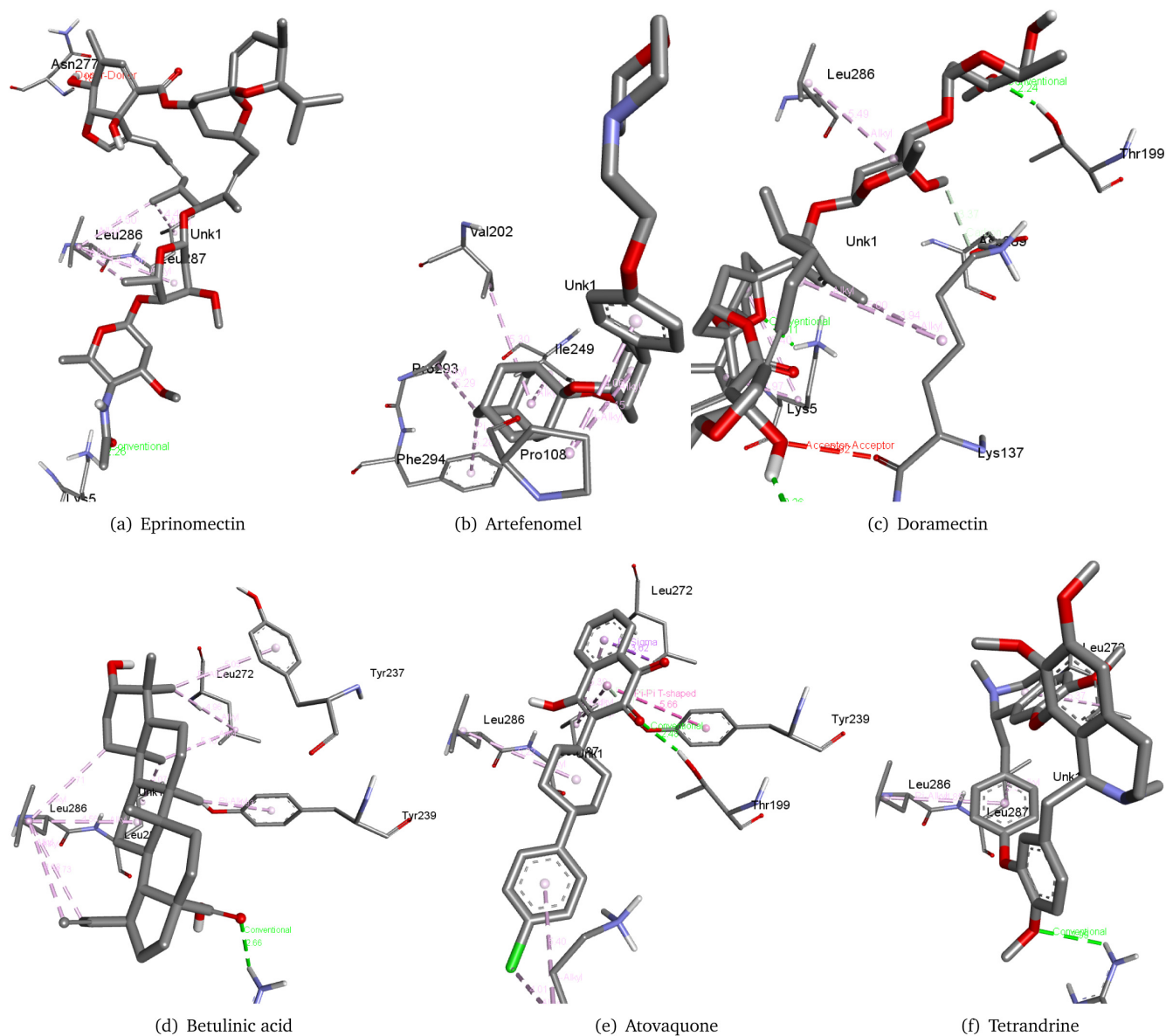
with their common name and ZINC ID sorted by ascending order of the free binding energy of the top 20 molecules from natural products database. The interaction of various molecules with the 6M03 main protease was studied. Allegra forms three hydrogen bonds with Thr111, Asn151, and Asp153 as well as interacts with Arg298, Val305, and Phe305 residues of 6M03 main protease. Baicalin forms four hydrogen bonds with Thr111, Thr292, Ile152, and Arg298 along with interacting with Asp153, Asn151, and Val303 residues of the main protease 6M03. Curine forms three hydrogen bonds with Arg131, Thr199, and Leu287 along with having interactions with Asp289, Leu286, and Tyr237 residues of 6m03 main protease. Etamidindole forms two hydrogen bonds with Thr111 and Asp295, it also interacts with Phe8, Phe294, Arg295, Arg298, and Pro252 residues of main protease 6M03. Glycyrrhetic acid forms a hydrogen bond with Lys137(2.24 Å) as well as interacts with Tyr237, Tyr239, Leu272, Leu286, and Leu287 residues of the main protease 6m03. Euphol interacts with Phe8, Val297, Arg298, and Val303 residues of the main protease. The interaction of few of the 20 molecules with the protein can be seen in [Figure 3](#). Full results are available in the *Extended data*<sup>12</sup>.

### Discussion

HTVS is one of the best methods for identifying molecules acting against drug targets in a very short time period, when compared to traditional drug identification strategies. Remdesivir was detected as COVID-19 inhibitory drug via virtual screening method<sup>6</sup>. Therefore, keeping the present scenario in our mind, we undertook this study to provide individuals with COVID-19 with drugs already available. Surprisingly, we have found good hits from the databases with medicinal properties.

Artefenomel is known to treat malaria and other parasitic diseases. Betulinic acid is under trial for the treatment of dysplastic nevus syndrome. Atovaquone is an approved drug for the treatment of *Pneumocystis carinii* pneumonia and malaria. Tetrandrine is in the experimental stage for anticancer, antimalarial, antiparasitic category. Eprinomectin and doramectin are veterinary antiparasitic drugs.

Many of the natural compounds identified have medicinal properties. Taraxerone has allelopathic and antifungal effect<sup>20</sup>, Morusin has anti-oxidant and anticancer properties<sup>21</sup>, RA VII compound is an antitumor agent<sup>22</sup>, and neoruscogenin is used against chronic venous disorders<sup>23</sup>. Justicidin D exhibits anti-inflammatory properties<sup>24</sup>, Licoricidin is an antimetastatic molecule<sup>25</sup> whereas euphol is used against asthma and cancer along with syphilis, and rheumatism<sup>26</sup>. Schisandrene has anti-oxidant activity<sup>27</sup>, curine is reported as a vasodilator<sup>27</sup>, angoluvarin has antimicrobial activity<sup>28</sup>, baicalin is used to treat cardiovascular diseases, inflammation and hypertension<sup>29</sup>. Glycyrrhetic acid shows anti-inflammatory, anti-ulcer,



**Figure 2.** Interaction of COVID-19 main protease 6M03 with ligands eprinomectin, artefenomel, doramectin, betulinic, atovaquone, and tetrandrine.

hepatoprotective, anti-allergic, anti-tumor, antioxidant and anti-diabetic activity<sup>30</sup>. Isomitrphylline has an antioxidant properties<sup>31</sup>, bikaverin and rutensin has anti-tumour activities<sup>32,33</sup>. Jolkinol B has anticancer properties<sup>34</sup> and Ethamidindole exhibits antihistamine properties<sup>35</sup>. Fexofenadine acetate, commonly known as Allegra, is an antihistamine pharmaceutical drug presently used in the treatment of allergy symptoms such as urticaria and hay fever<sup>36</sup>.

When we compared our two datasets, we found that majority of the molecules showed lesser free binding energy as compared to the reference molecules as in [Table 1](#), [Table 2](#), and [Table 3](#). Surprisingly, we obtained good hits from our natural database which is good news since after observing their interaction and biotherapeutic functions, we might have achieved our COVID-19 inhibitory drugs. One such drug from natural database is fexofenadine acetate (Allegra) which is pres-

**Table 3. Docking of natural compounds for probable COVID-19 inhibitory activity.**

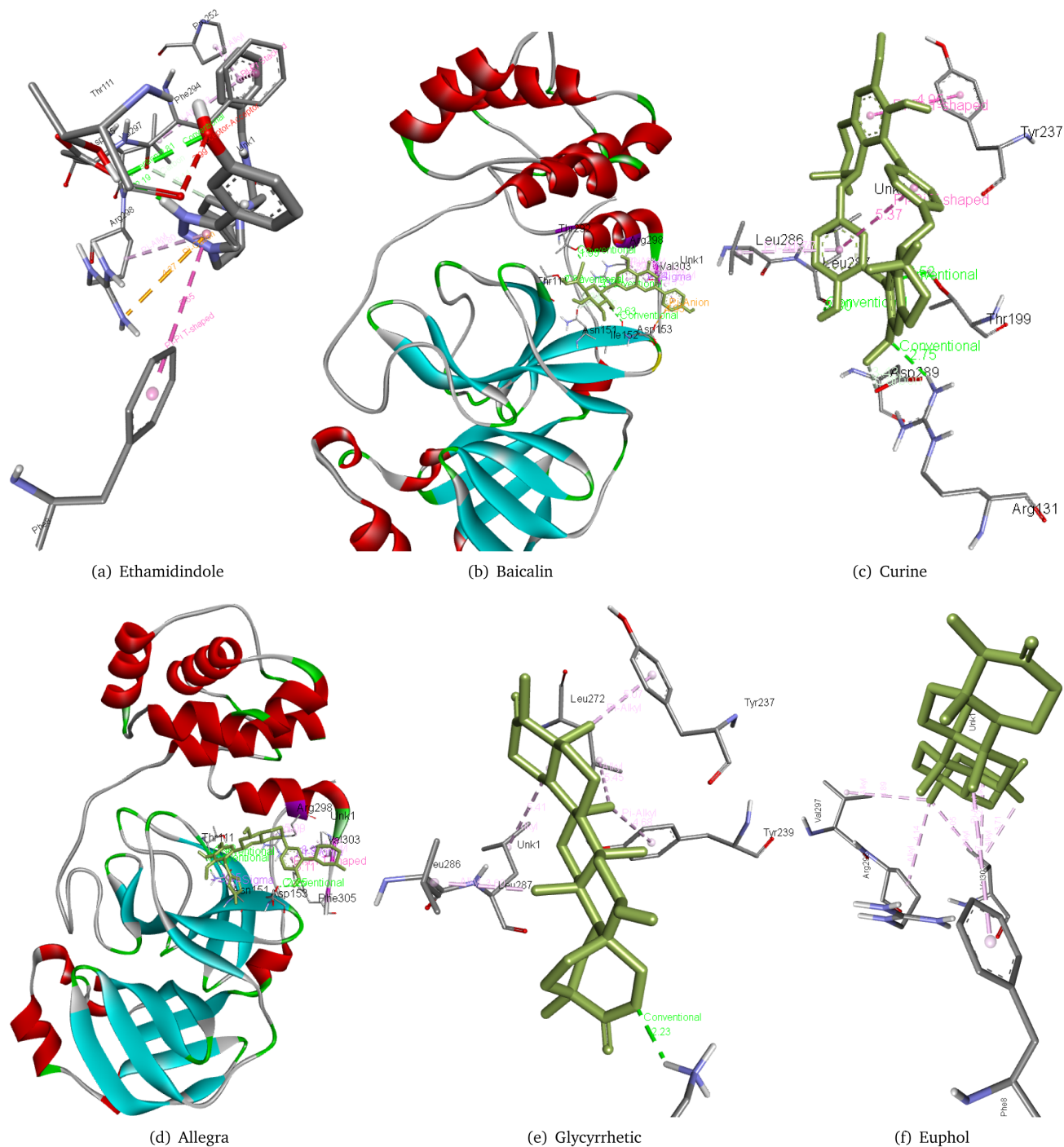
	ZINC Prefix: ZINC000 ID	Common name	Binding energy kcal/mol
1	085592428	Furobinordentatin	-9.9
2	085592420	Alstiphyllanine F	-9.8
3	004104836	Taraxerone	-9.6
4	085593550	Morusin	-9.6
5	085596349	Fexofenadine acetate (Allegra)	-9.6
6	085648318	RA VII compound	-9.4
7	253589870	Neoruscogenin	-9.3
8	006627242	Justicidin D / neojusticidin A	-9.3
9	005742262	Licoricidin	-9.2
10	085643829	Euphol	-9.2
11	085593537	Schisandrene	-9.2
12	029483258	Curine	-9.1
13	005808583	Bikaverin	-9.1
14	014966151	Angoluvarin	-9.1
15	013543704	Baicalin	-9.1
16	085642858	Glycyrrhetic acid	-9.1
17	004995171	Isomitraphylline	-9
18	008829747	Rutarensin	-8.9
19	034075173	Jolkinol B	-8.9
20	003838672	Ethamidindole	-8.9

ently in use as anti-allergic medicine. We also have hits from 129 drugs but there is one, atovaquone, which is presently used against pneumonia and malaria and also a very good candidate for COVID-19 treatment.

### Conclusions

The best therapeutic drugs inferred from our studies are atovaquone, fexofenadine acetate (Allegra), justicidin D, baicalin, glycyrrhetic acid and ethamidindole based on their docking score, interaction studies and their present applications for probable COVID-19 treatment. The rest of the molecules could also be used as COVID-19 inhibitory drugs after further evaluation. When we compared our data with reference molecules score of currently in use drug against COVID-19,

we found that atovaquone showed better binding energy than hydroxychloroquine and remdesivir. It is one of the best drug candidate for COVID-19 treatment since it is already in use for treating *Pneumocystis carinii* pneumonia and malaria. Fexofenadine acetate is another good target drug for COVID-19 treatment since it is naturally derived and presently used for its anti-histamine properties. Ethamidindole could possibly act as COVID-19 inhibitor since it is reported as anti-histamine and this novel virus activates cytokine secretion in human body. part from these, anti-inflammatory natural molecules such as justicidin D, baicalin, and glycyrrhetic acid could work against COVID-19 since SARS-CoV-2 virus induces inflammation. The rest of the top 20 molecules could also be considered since they all have some medicinal properties as explained above.



**Figure 3.** Interaction of six of the top 20 hits from Zinc natural database with main protease 6m03.

#### Data availability

##### Source data

The COVID-19 main protease structure was downloaded from the Protein Data Bank, ID 6M03: <https://www.rcsb.org/structure/6M03>.

Ligands were obtained from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) and the Zinc Natural Products database (<http://zinc.docking.org/>).

#### Extended data

Zenodo: Molecular docking COVID-19. <https://doi.org/10.5281/zenodo.3840625><sup>12</sup>.

This project contains the following extended data:

- Drugs repurposing list (PDF). (PubChem CID of each ligand along with the minimized energy of each molecule and binding affinity results)



- Drugs (subfolder). (Interaction images of the reference molecules as well as the best performing target molecules from the 129 docked drugs.)
- Natural compounds (subfolder). (Interaction images of the best performing target molecules from the Zinc Natural Products database.)
- Results (PDF). (Complete docking results from the Zinc Natural Products database and the list of 129 drugs.)

Extended data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

## Acknowledgements

The authors would like to thank members of the research group *ITI* for their valuable feedback.

## References

- Xu X, Chen P, Wang J, *et al.*: Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Science China Life Sciences*. 2020; **63**(3): 457–460. [PubMed Abstract](#) | [Publisher Full Text](#)
- Zhu N, Zhang D, Wang W, *et al.*: A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020; **382**(8): 727–733. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- World Health Organization: Coronavirus disease 2019 (COVID-19) Situation Report - 101, 2020. [Reference Source](#)
- Jiang F, Deng L, Zhang L, *et al.*: Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). *J Gen Intern Med*. 2020; **35**(5): 1545–1549. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Chang YC, Tung YA, Lee KH, *et al.*: Potential therapeutic agents for COVID-19 based on the analysis of protease and RNA polymerase docking. *Preprints*. 2020; 2020020242. [PubMed Abstract](#) | [Publisher Full Text](#)
- Hall DC Jr, Ji HF: A search for medications to treat covid-19 via *in silico* molecular docking models of the sars-cov-2 spike glycoprotein and 3cl protease. *Travel Med Infect Dis*. 2020; 101646. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Jacob RB, Andersen T, McDougal OM: Accessible high-throughput virtual screening molecular docking software for students and educators. *PLoS Comput Biol*. 2012; **8**(5): e1002499. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Lengauer T, Rarey M: Computational methods for biomolecular docking. *Curr Opin Struct Biol*. 1996; **6**(3): 402–406. [PubMed Abstract](#) | [Publisher Full Text](#)
- Salvaterra K, Florez H: Bioinformatics approach to analyze influenza viruses. In *Workshop on Engineering Applications*. Springer, 2018; 442–452. [Reference Source](#)
- Goldman BB, Wipke WT: Qsd quadratic shape descriptors. 2. molecular docking using quadratic shape descriptors (qsdock). *Proteins*. 2000; **38**(1): 79–94. [PubMed Abstract](#)
- Feig M, Onufriev A, Lee MS, *et al.*: Performance comparison of generalized born and poisson methods in the calculation of electrostatic solvation energies for protein structures. *J Comput Chem*. 2004; **25**(2): 265–284. [PubMed Abstract](#) | [Publisher Full Text](#)
- Singh S, Florez H: Molecular docking covid-19. 2020. <http://www.doi.org/10.5281/zenodo.3840625>
- Salvaterra K, Vera M, Florez H: Bioinformatics methods to discover antivirals against zika virus. In *International Conference on Applied Informatics*. Springer, 2019; 3–14. [PubMed Abstract](#) | [Publisher Full Text](#)
- Hector F, Karina S: Bioinformatics study of mutations of resistance to antivirals in the ns5a gen of hcv. *International Information Institute (Tokyo). Information*. 2017; **20**(9A): 6665–6672. [Reference Source](#)
- Farhadi T, Fakharian A, Ovchinnikov RS: Virtual screening for potential inhibitors of ctx-m-15 protein of klebsiella pneumoniae. *Interdiscip Sci*. 2018; **10**(4): 694–703. [PubMed Abstract](#) | [Publisher Full Text](#)
- Rathi S, Ish P, Kalantri A, *et al.*: Hydroxychloroquine prophylaxis for covid-19 contacts in india. *Lancet Infect Dis*. 2020; S1473-3099(20)30313-3. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Meo SA, Klonoff DC, Akram J: Efficacy of chloroquine and hydroxychloroquine in the treatment of covid-19. *Eur Rev Med Pharmacol Sci*. 2020; **24**(8): 4539–4547. [PubMed Abstract](#) | [Publisher Full Text](#)
- Wang Y, Zhang D, Du G, *et al.*: Remdesivir in adults with severe covid-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2020; **395**(10236): 1569–1578. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Caly L, Druce JD, Catton MG, *et al.*: The fda-approved drug ivermectin inhibits the replication of sars-cov-2 *in vitro*. *Antiviral res*. 2020; **178**: 104787. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Saha D, Dasgupta S, Saha A: Antifungal activity of some plant extracts against fungal pathogens of tea (*Camellia sinensis*). *Pharma Biol*. 2005; **43**(1): 87–91. [PubMed Abstract](#) | [Publisher Full Text](#)
- Ding B, Lv Y, Zhang YQ: Anti-tumor effect of morusin from the branch bark of cultivated mulberry in bel-7402 cells via the mapk pathway. *RSC Adv*. 2016; **6**(21): 17396–17404. [PubMed Abstract](#) | [Publisher Full Text](#)
- Bigot A, Dau MET, Zhu J: Total synthesis of an antitumor agent ra-vii via an efficient preparation of cycloisodityrosine. *J Org Chem*. 1999; **64**(17): 6283–6296. [PubMed Abstract](#) | [Publisher Full Text](#)
- Helleboid S, Haug C, Lamotte K, *et al.*: The identification of naturally occurring neoruscogenin as a bioavailable, potent, and high-affinity agonist of the nuclear receptor rora. (nr1f1). *J Biomol Screen*. 2014; **19**(3): 399–406. [PubMed Abstract](#) | [Publisher Full Text](#)
- Fukamiya N, Lee KH: Antitumor agents, 81. justicidin-a and diphyllin, two cytotoxic principles from justicia procumbens. *J Nat Prod*. 1986; **49**(2): 348–350. [PubMed Abstract](#) | [Publisher Full Text](#)
- Park SY, Lim SS, Kim JK, *et al.*: Hexane-ethanol extract of *Glycyrrhiza uralensis* containing licoricidin inhibits the metastatic capacity of du145 human prostate cancer cells. *Br J Nutr*. 2010; **104**(9): 1272–1282. [PubMed Abstract](#) | [Publisher Full Text](#)
- Mali PY, Shital S: *Euphorbia tirucalli* L.: Review on morphology, medicinal uses, phytochemistry and pharmacological activities. *Asian Pac J Trop Biomed*. 2017; **7**(7): 603–613. [PubMed Abstract](#) | [Publisher Full Text](#)
- Choi YW, Takamatsu S, Khan SI, *et al.*: Schisandrene, a dibenzocyclooctadiene lignan from *Schisandra chinensis*: structure-antioxidant activity relationships of dibenzocyclooctadiene lignans. *J Nat Prod*. 2006; **69**(3): 356–359. [PubMed Abstract](#) | [Publisher Full Text](#)
- Hufford CD, Oguntimein BO, Shoolery JN: Angoluarin, an antimicrobial dihydrochalcone from uvaria angolensis. *J Org Chem*. 1987; **52**(23): 5286–5288. [PubMed Abstract](#) | [Publisher Full Text](#)
- Ding L, Jia C, Zhang Y, *et al.*: Baicalin relaxes vascular smooth muscle and lowers blood pressure in spontaneously hypertensive rats. *Biomed Pharmacother*. 2019; **111**: 325–330. [PubMed Abstract](#) | [Publisher Full Text](#)
- Kao TC, Shyu MH, Yen GC: Glycyrrhizic acid and 18 $\beta$ -glycyrrhetic acid inhibit inflammation via pi3k/akt/gsk3 $\beta$  signaling and glucocorticoid receptor activation. *J Agric Food Chem*. 2010; **58**(15): 8623–8629. [PubMed Abstract](#) | [Publisher Full Text](#)
- Azevedo B, Roxo M, Borges M, *et al.*: Antioxidant activity of an aqueous leaf extract from *Uncaria tomentosa* and its major alkaloids mitraphylline and isomitraphylline in *Caenorhabditis elegans*. *Molecules*. 2019; **24**(18): 3299. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Limón MC, Rodríguez-Ortiz R, Avalos J: Bikaverin production and applications. *Appl Microbiol Biotechnol*. 2010; **87**(1): 21–29. [PubMed Abstract](#) | [Publisher Full Text](#)
- Yang QY, Tian XY, Fang WS: Bioactive coumarins from *Boenninghausenia sessilicarpa*. *J Asian Nat Prod Res*. 2007; **9**(1): 59–65. [PubMed Abstract](#) | [Publisher Full Text](#)
- Lage H, Duarte N, Coburger C: Antitumor activity of terpenoids against classical and atypical multidrug resistant cancer cells. *Phytomedicine*. 2009; **17**(6): 441–8. [PubMed Abstract](#) | [Publisher Full Text](#)
- Patnaik GK, Das PK, Dhawan BN, *et al.*: Pharmacology of ethamidindole, a new antihistaminic agent. *Indian J Pharmacol*. 1979; **11**(3): 181–187. [Reference Source](#)
- Kumar L, Shahnwaj Alam Md, Lal Meena C, *et al.*: Fexofenadine hydrochloride. *Profiles of drug substances, excipients and related methodology*. 2009; **34**: 153–192. Elsevier. [Reference Source](#)

# Open Peer Review

Current Peer Review Status: ? ✓ ?

---

## Version 1

Reviewer Report 14 July 2020

<https://doi.org/10.5256/f1000research.26715.r67037>

© 2020 Ghosh P. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



**Pritha Ghosh** 

Laboratory of Bioinformatics and Protein Engineering, International Institute of Molecular and Cell Biology in Warsaw, Warsaw, 02-109, Poland

The manuscript by Singh and Florez presents the discovery of drugs against COVID19 using molecular docking methods.

### Major:

1. The authors must discuss in further detail as to how this work compares with other published reports of drugs targeted against SARS-CoV-2.
2. The authors should cite references for the results mentioned in the Introduction section of the manuscript.
3. How was the -6 kcal/mol free binding energy cut-off selected? As I understand this is not the lowest, the highest or the average of the reference molecule binding energies. Then what is the basis for the selection of this cut-off value?
4. The authors have discussed the docking results for the reference and the test molecules independently, but have not provided a comprehensive comparison of the observations. In my opinion, such a comparison is necessary for assessing the effectivity of the new drugs as compared to the existing drugs. The authors have also not discussed the importance of the residues Tyr237, Leu272, Leu287 etc. Are these known to be critical residues in the functioning of the main protease?

### Minor:

1. The statistics on the number of cases and deaths need to be updated before the indexing.
2. The authors should be more careful about the technicalities mentioned in the paper. For example, "6m03" has been mentioned loosely in the Introduction section without pointing to the fact that it is a PDB structure; the HTVS abbreviation has not been introduced in the manuscript before the first instance of its use.

The paper requires English editing by a professional and/or a native English speaker.

**Is the work clearly and accurately presented and does it cite the current literature?**

Partly

**Is the study design appropriate and is the work technically sound?**

Partly

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Not applicable

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Bioinformatics and Genomics

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Reviewer Report 06 July 2020

<https://doi.org/10.5256/f1000research.26715.r64264>

© 2020 Yepes-Calderon F. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



**Fernando Yepes-Calderon** 

<sup>1</sup> Division of Neurosurgery, Children's Hospital Los Angeles, Los Angeles, CA, USA

<sup>2</sup> SBP LLC, Reserach and Development, Fort Pierce, FL, USA

The paper is of interest under the current cov2 pandemic. Simulation of the strength of the bonds between molecules can identify inhibitors without human subjects' need to test. This paper did not focus on finding new compounds but in examining those present in existing medicine. This approach expedites the process of finding a cure, and the suggestions done are well-founded. Overall, the materials and methods section is exhaustive and asserts reproducibility.

There are some wordy paragraphs with redundancies. Please take a look at the following one and the replacement that I suggest.

Original> The transmission of this coronavirus occurs due to the binding of the CoV spike protein to the angiotensin converting enzyme 2 (ACE2) receptor present on the cell surface of the human host.

Suggestion>The transmission of this coronavirus occurs due to the binding of the CoV spike protein to the angiotensin-converting enzyme 2 (ACE2) receptor present on the human host's cell surface.

I might suggest the authors remark the differences between their approach and the one presented by:

Suyash Pant, Peptide-like and small-molecule inhibitors against Covid-19<sup>1</sup>

It could be included in the discussion.

### References

1. Pant S, Singh M, Ravichandiran V, Murty USN, et al.: Peptide-like and small-molecule inhibitors against Covid-19. *J Biomol Struct Dyn*. 2020. 1-10 [PubMed Abstract](#) | [Publisher Full Text](#)

**Is the work clearly and accurately presented and does it cite the current literature?**

Partly

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Not applicable

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Methods in medicine, Medical Imaging, Artificial Intelligence

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Reviewer Report 29 June 2020

<https://doi.org/10.5256/f1000research.26715.r64263>

© 2020 Castillo E. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**Elio Rodrigo Castillo**

Laboratorio de Genética Evolutiva, Instituto de Biología Subtropical (IBS), FCEQyN, CONICET-UNaM, Posadas, Argentina

I think that all the data is a quite good contribution, but in my opinion, text should be deeply modified to be more attractive to the readers and to point more directly their main objective.

**Introduction**

**Paragraph 2:** I suggest the authors to focus in the evidences showed by Chang *et al.* We know that vaccines are not available for COVID yet but your aim is to identify **potential** drugs for treatment.

**Paragraph 3:** Move this paragraph below “*The World Health Organization (WHO) declared this disease as a pandemic on 11th March, 2020 and SARS-CoV-2 as the deadliest virus till date on earth claiming 217,896 deaths till 30th April, 2020*”.

**Paragraph 4:** Please remove this paragraph because is not discussed in the corresponding section.

**Paragraph 5:** I recommend the authors to rewrite this paragraph. Authors performed an approach for searching drugs candidates based on databases. Please, focus in the main objective of the work. In my opinion authors could highlight the importance of bioinformatic tools (docking as the first approach) using available databases. I suggest to rewrite this paragraph because most of it content correspond to the Methodology section.

**Methods**

In my opinion authors should be more clear with the methodology. You could cite a work in the introduction section where docking was the better strategy for drugs candidates search. In this section, you should explain your criteria of protein selection, provide a list and finally, the docking process. I suggest to reorganize this section as:

"Molecule selection and processing (or edition)" and "Molecular docking". In my opinion it is not necessary to split this information.

**Results**

For a better understanding, I strongly recommend to use a general graphical scheme explaining the selection, the macromolecules edition, and the pipe used for the docking analysis.

I suggest to focus only in the docking results against different ligands (from databases, natural etc). Some sentences correspond to the discussion section.

**Discussion**

It is not clear if you work with information from databases or with clinical samples. Please, rewrite this sentence.

The paragraph underline (2nd) is disconnected from this section, please review.

In my opinion the third paragraph of this section is not necessary. Authors could write in a sentence all this information and cite.

I also suggest to discuss better your results and make a contrast with the available bibliography;

authors repeated in this section the results. I understand that your contribution is relevant but from other perspective: bioinformatic tools for a quick detection of potential antivirals or drugs, using as an example the COVID.

Several papers cited in the introduction section are not discussed.

### **Conclusions**

I suggest the integration of this section with the discussion. Authors proposed several treatments, inferred from HTVS, however, you should be careful with your statements. I recommend to discuss and compare the variables or data as indicators for potential treatments.

**The manuscript is written with understandable English, though some English revision is necessary.**

**In my opinion, after several major revisions and reorganization of the text, the study will be acceptable for indexing on F1000Research.**

**Is the work clearly and accurately presented and does it cite the current literature?**

Partly

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

I cannot comment. A qualified statistician is required.

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Partly

***Competing Interests:*** No competing interests were disclosed.

***Reviewer Expertise:*** Evolutionary Biology, Genomics

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

---

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact [research@f1000.com](mailto:research@f1000.com)

**F1000Research**