Current Bioinformatics, 2021, *16*, 1320-1327

RESEARCH ARTICLE

Identification of Potential Inhibitors Against SARS-CoV-2 Using Computational Drug Repurposing Study

Hasan Zulfiqar[1], Fu-Ying Dao[1], Hao Lv[1], Hui Yang[1], Peng Zhou[1], Wei Chen[2,*] and Hao Lin[1,*]

[1]*School of Life Science and Technology and Center for Informational Biology, University of Electronic Science and Technology of China, Chengdu 610054, China;* [2]*Center for Genomics and Computational Biology, School of Life Sciences, North China University of Science and Technology, Chengdu, China*

ARTICLE HISTORY

Received: November 03, 2020
Revised: March 13, 2021
Accepted: March 30, 2021

DOI:
10.2174/1574893616666210726155903

Abstract: ***Background*:** SARS-Cov-2 is a newly emerged coronavirus and causes a severe type of pneumonia in the host organism. So, it is an urgent need to find some inhibitors against SARS-Cov-2. Therefore, drug repurposing study is an effective strategy for treating pneumonia to find the inhibitors of SARS-Cov-2 proteins.

***Methods*:** For this purpose, a library of 2500 verified drug chemical compounds was generated and the compounds were docked against Nucleocapsid, Membrane and Envelope protein structures of SARS-Cov-2 to determine the binding affinity of the chemical compounds against targeting binding pockets. Moreover, cheminformatics properties and ADMET of these compounds were assessed to find the drug-likeness behavior of compounds. The chemical compounds with the lowest S-score were identified as potential inhibitors.

***Results*:** Our findings showed that the compound ids 1212, 1019 and 1992 could interact inside the active sites of membrane protein, nucleocapsid protein and envelope protein.

***Conclusion*:** This *in silico* knowledge will be helpful for the design of novel, safe and less expensive drugs against the SARS-Cov-2.

Keywords: Molecular docking, SARS-Cov-2, COVID-19, inhibitors, protein, drug.

1. INTRODUCTION

Recently, a novel coronavirus called SARS-Cov-2 [1] has emerged and caused a major pneumonia outbreak in the world. As of April 12, 2020, there were more than 1,780,000 COVID-19 [2] infected patients in the world with more than 108,850 deaths. In the current pandemic situation, understanding the mechanism of viral infections and their inhibition are of high urgency for the control and treatment of SARS-Cov-2 caused COVID-19 disease. Some pre-existing anti-viral drugs are now under clinical trials [3-5]. The investigation of the mode of action and mechanism of the viral infection, cell recognition and entry of the virus is the most crucial step which will help determine viral infectivity and pathogenesis [6]. Coronavirus usually uses spike glycoprotein to interact with the human respiratory and epithelial cells expressing angiotensin–converting enzyme-2 receptor [7, 8]. Four kinds of proteins, Nucleocapsid protein, Envelope protein, Membrane protein and Spike protein, have important functions in SARS-Cov-2, and are shown in Fig. (**1**) [9]. Therefore, for the understanding of viral infection, it is necessary to first understand the mechanisms of these proteins. Scientists have applied different methodologies such as siRNA [10-12], miRNA [13] and CRISPR/cas9 [14] for the treatment of COVID-19 disease. The origin of the replication site of the coronavirus in the host cell was found and replaced by the malicious genes using gene-editing technique [15].

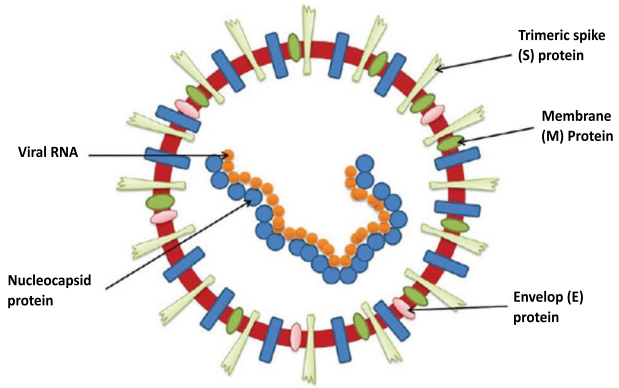

Fig. (1). An illustration of SARS-Cov-2. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

*Address correspondence to these authors at Center for Genomics and Computational Biology, North China University of Science and Technology, Tangshan, China; E-mail: chenweiimu@gmail.com; School of Life Science and Technology and Center for Informational Biology, University of Electronic Science and Technology of China, Chengdu 610054, China; Tel/Fax: +86-13678168394; E-mail: hlin@uestc.edu.cn

2212-392X/21 $65.00+.00

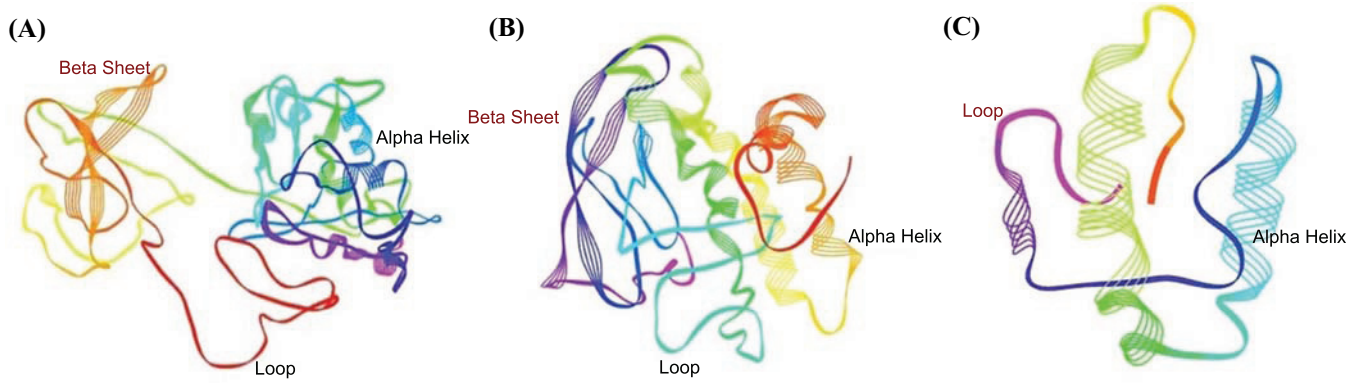

Fig. (2). The computational predicted structures of three proteins; (**A**) N-protein, (**B**) M-protein, (**C**) E-protein. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Here, we took three proteins, Nucleocapsid, Membrane and Envelop proteins (N protein, M protein and E protein) as targets to identify the potent inhibitors by using *in silico* molecular docking procedures [16, 17] because these three proteins have a vital role in assembly activities, morphogenesis and replication, and only a few works have focused on these proteins. N protein is the innermost protein of the SARS-Cov-2 and plays a very important role during the virions assembly through its interactions with the genome of the virus and other membrane proteins. It plays a fundamental role in increasing the efficiency of the transcription and replication of the viral genome and also packages the viral RNA positive-strand into helical ribonucleocapsid form. M protein is the outer membrane protein located on the surface of the SARS-Cov-2 and also the main component of the viral envelope. It plays a very important role in morphogenesis through its interaction with other viral proteins. E protein plays a main role in morphogenesis and assembly activities. It also plays a central role in the induction of apoptosis and activates the host inflammasomes, leading to IL-1beta overproduction. E protein also acts like a viroporin and self assembles in the host membrane, forming pentameric protein-ligand pores that allow the ion transport from outside surface to the inside of the viral genome. These proteins have vital roles in the whole SARS-Cov-2. However, there is no study available for their inhibition as compared to the Spike proteins. Therefore, we applied molecular docking approach to identify the best inhibitors against N, M and E proteins of the SARS-Cov-2 in order to provide a guide for curing the COVID-19 pneumonia diseases.

In this paper, we performed computer-based screening of verified compound chemicals for the identification of potential inhibitors against SARS-Cov-2. *In silico* studies and molecular docking procedures were performed on compounds to find the binding pocket inside the active sites of the N, M and E proteins. The chemoinformatic properties and ADMET properties of the compounds were also analyzed to check the adsorption, absorption and toxicity of the compounds inhibitors. The detailed structures of Nucleocapsid protein, Membrane protein and Enveloped protein could give us possible binding sites where compounds (inhibitors) possibly bind. It may provide us with a good prediction of compounds that attach well in the N, M and E proteins active sites. The molecular docking was performed to study the binding between compounds and N, M and E proteins by using the PyRx software. We analyzed the results through the reliable Discovery studio.

2. MATERIALS AND METHODS

2.1. Compound Structures and Receptor Proteins

Experimentally verified Chemical drug compounds were collected from the online database Pubchem [18] and ZINC 15 [19], (http://zinc15.docking.org/). A structure library including 2,500 verified drug chemicals was generated in the PyRx software [20] (https://pyrx.sourceforge.io/), and the compounds were regarded as the potential inhibitors against N, M and E proteins of SARS-Cov-2. The structure library of 2500 compounds is freely available in Supplementary file **1**. The structures of compounds were drawn by using the Chem Draw software [21]. Three-dimensional structures of computational verified N, M and E proteins were extracted from (https://zhanglab.ccmb.med.umich.edu/C-I-TASSER/2019-nCov/) and are shown in Fig. (**2**). The active sites of the N, M and E proteins were found using a reliable CASTp 3.0 [22] online server. The binding interactions inside the binding pocket and the Molecular docking between chemical compounds and proteins were analyzed by using Discovery studio [17, 23].

2.2. Chemoinformatic Properties of Compounds

Chemoinformatic characteristics of chemical compounds (Molecular weight, Molecular Volume, Log P, HBD and PSA (A2)) were checked using molinspiration (https://www.molinspiration.com). The chemical compounds were evaluated on the basis of their chemoinformatic properties by using the Lipinski rule of five [24].

2.3. ADMET Properties of Compounds

The chemical compounds were checked for ADMET properties using the ADMET analysis. The prediction of ADMET properties plays a crucial role in finding effective drugs and also helps to eliminate unwanted compounds in

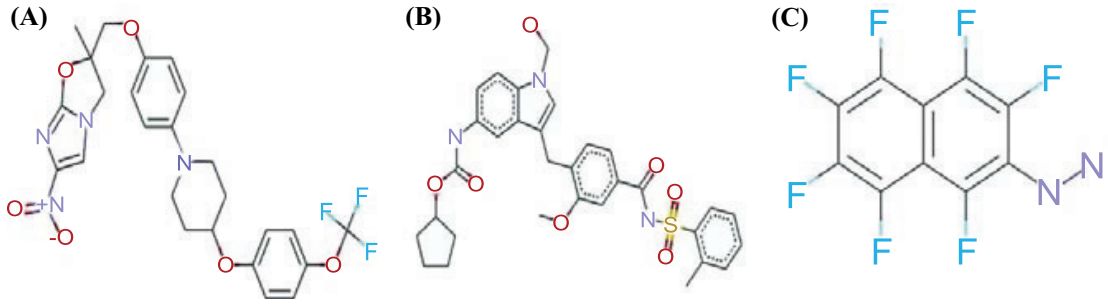

Fig. (3). The three compound structures. (**A**), the compound structure id is 1019. (**B**), the compound structure id is 1212. (**C**), the compound structure id is 1992.

Table 1. The optimal chemical compounds against NME proteins of SARS-Cov-2.

Compound ID	S-score	Rmsd (lb)	Rmsd (ub)	Receptor Residues	Interaction	Refs.
1019 for N protein	-11.5	0.0	0.0	Asn77,Asp144,Lys143,Gly147,Thr49,Pro117,Tyr112	H-Pi,HAccp,H-don	[26-29]
1212 for M protein	-11.6	0.0	0.0	Trp31,Leu35,Asn43,Tyr47,Ile40,Lys50	H-don,H-pi	[30-33]
1992 for E protein	-10.8	0.0	0.0	Lys53,Ser50,Leu37,Ala41,Asn48	H-Accp,H-don	[34]
Peptidomimetic[(a)]	-10.3	0.0	0.0	Lys143,Gly147,Asn48,Leu35,Asp158,Asn79,Tyr117	H-Accp, H-don	[35]

(a): Peptidomimetic is used as a reference.

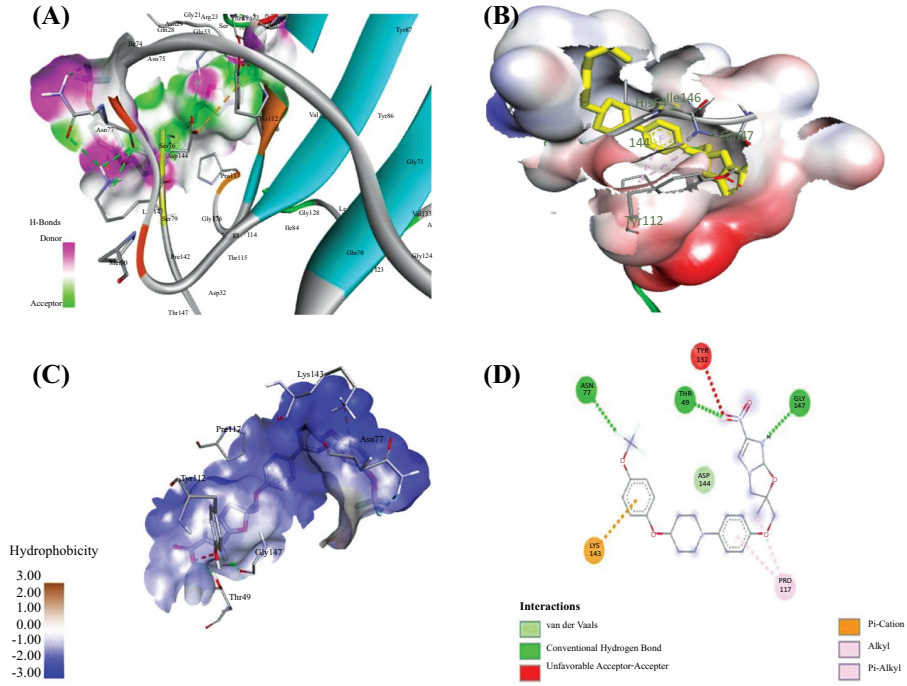

Fig. (4). (**A**), Binding interaction of compound id 1019 with N-protein. (**B**), Closed interaction inside the binding pocket. (**C**), Hydrophobic region. (**D**), 2D interaction between N-protein and compound id 1019. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

the early steps of drug designing. The absorption, distribution, metabolism, excretion and toxic properties of compounds were evaluated using the freely available online server PKCSM [25].

3. RESULTS AND DISCUSSION

The molecular docking was performed to investigate the binding interaction between 2,500 chemical compounds and N, M, E protein structures of SARS-Cov-2. Chemical compounds with the lowest S-score values against N, M, E proteins of SARS-Cov-2 are shown in Table **1** [26-35]. Their structures are shown in Fig. (**3**). These compounds are regarded as the best compounds because they could bind receptors with high binding energy.

From Table **1**, it can be noticed that the compound id 1019 has the lowest "S-score" value against N-protein. The binding interaction of compound id 1019 with N-protein, their closed interaction inside the binding pocket, their hydrophobic region and 2-dimensional interactions are shown in Fig. (**4**). Other four chemical compounds ids 1370, 1470,

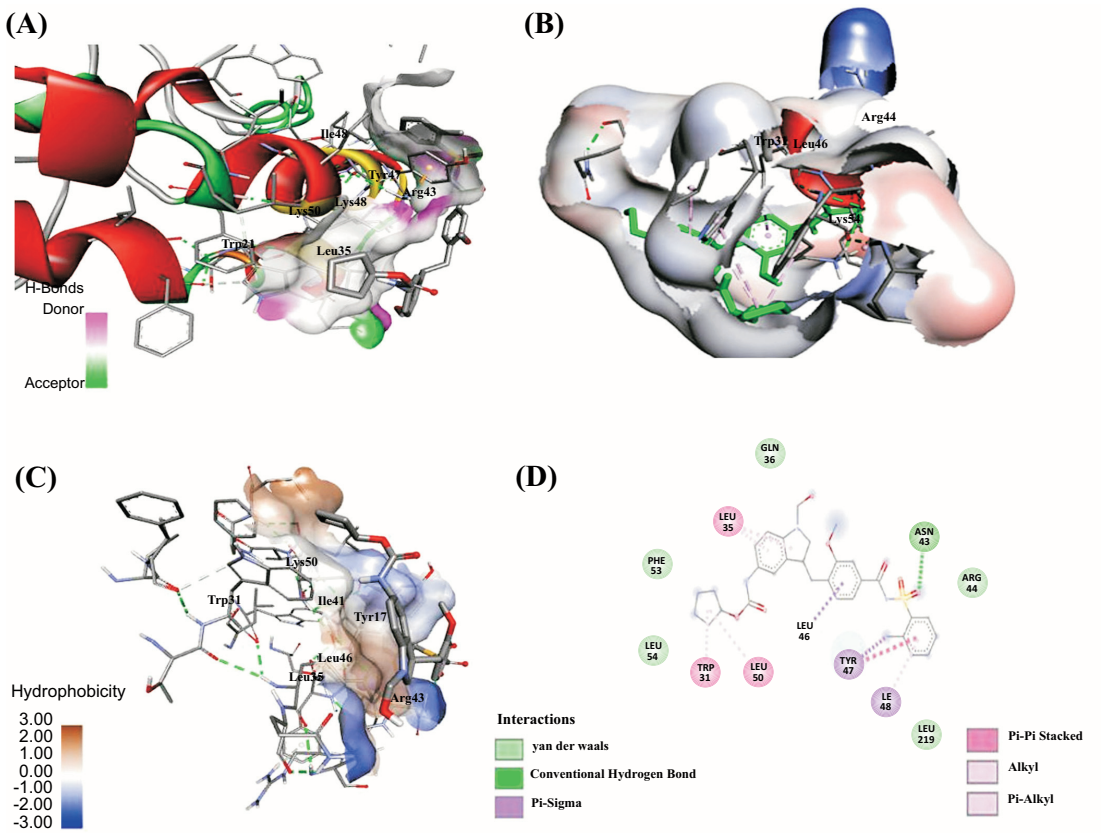

Fig. (5). (**A**), Binding interaction of compound id 1212 with M-protein. (**B**), Closed interaction inside the binding pocket. (**C**), Hydrophobic region. (**D**), 2D interaction between M-protein and compound id 1212. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

1987 and 1021 also showed a lower "S-score" from the whole library and exhibited maximum binding interaction with this protein. The residues Asn77, Asp144, Lys143, Gly147, Thr49, Pro117 and Tyr112 could interact with the hydroxyl group and (O) group of the N-protein. And the compound id 1212 exhibited the lowest "S-score" value against M-protein. The binding interaction of compound id 1212 with M-protein, their closed interaction inside the binding pocket, their hydrophobic region and 2-dimensional interactions are shown in Fig. (**5**). Other four chemical compounds ids 1350, 1370, 2187 and 621 also showed lower "S-score" from the whole library and exhibited maximum binding interaction with this protein. The residues Trp31, Leu35, Asn43, Tyr47, Ile40 and Lys50 could interact with the hydroxyl group and (O) group of M-protein. The compound id 1992 has shown the lowest "S-score" value against E-protein. The binding interaction of compound id 1992 with E-protein, their closed interaction inside the binding pocket, their hydrophobic region and 2-dimensional interactions are shown in Fig. (**6**). Other four chemical compounds 1150, 1721, 2047 and 221 also showed lower "S-score" from the whole library and exhibited maximum binding interaction with this protein. The residues Lys53, Ser50, Leu37, Ala41 and Asn48 could interact with the hydroxyl group and (O) group of E-protein. Furthermore, the "S-score" and Rmsd values of the whole library of 2500 chemical compounds against N, M and E proteins are recorded in Table **S1** in Supplementary file 1.

The chemoinformatic properties and Lipinski rule of 5 of three compounds with the lowest S-score were also evaluated using the online server mol inspiration. It is believed that the compounds which follow the Lipinski rule of five are very good candidates for drug.

The chemoinformatic results of test compounds presented in Table **2** show that they follow the Lipinski rule of five very well. The values of the test compounds were found to be in between the standard values. This shows that these compounds might be a good target for drug designing. The Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) characteristics of the compounds were also evaluated using the online server pKCSM which is a tool to check the pharmacokinetic properties of the compounds. In Table **3**, it was found that compounds had good absorption values which showed the drug-likeness behavior of compounds, and distribution values were also good which showed that these compounds could penetrate through any barrier and reach the target receptor molecule.

The ADMET properties also show that the compounds are very less toxic which makes them a favorable target for drug designing. The computational and *in silico* studies show that these chemical compounds have good potential to inhibit the activity of SARS-Cov-2. The chemoinformatic properties and Lipinski rule of five indicate the less toxicity of compounds and drug-likeness behavior of the compounds.

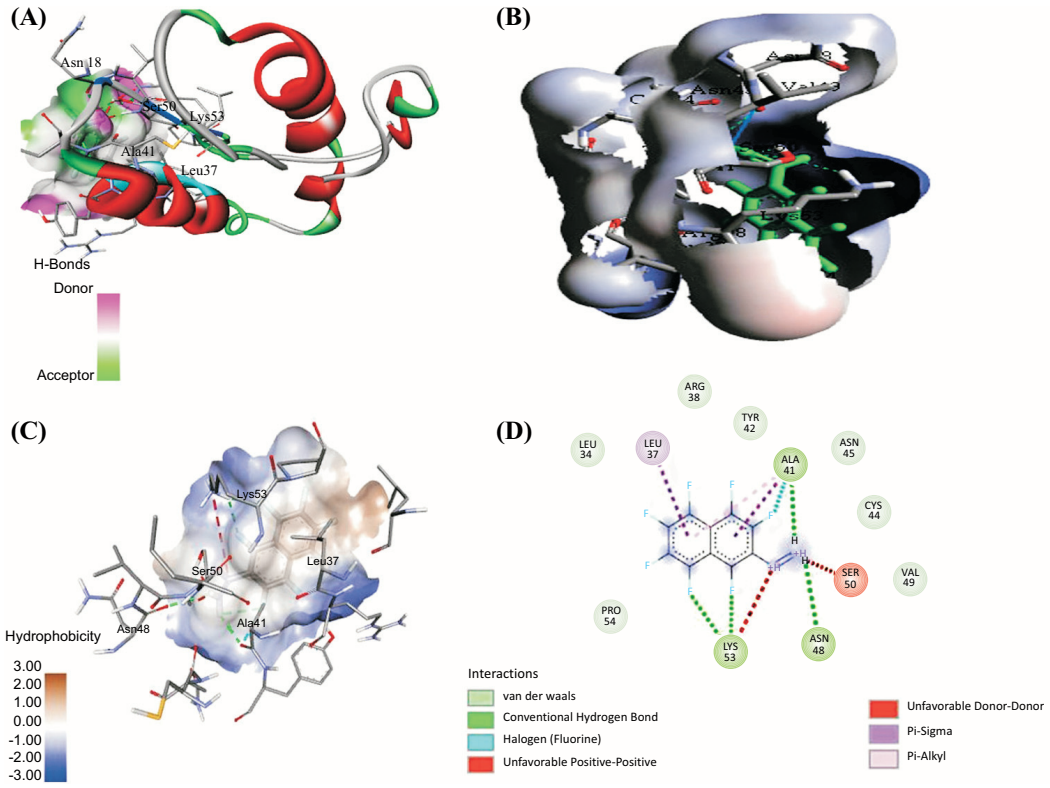

Fig. (6). (**A**), Binding interaction of compound id 1992 with E-protein. (**B**), Closed interaction inside the binding pocket. (**C**), Hydrophobic region. (**D**), 2D interaction between M-protein and compound id 1992. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Table 2. The chemoinformatic properties of the three compounds.

Compound Id	MW	HBD	Log P	Mol Vol	Violation	PSA (A2)
1019 for N-protein	534	0	5.61	449.89	1	129.56
1212 for M-protein	575	2	5.50	499.89	1	149.56
1992 for E-protein	284	2	3.10	470.62	0	367.37

Table 3. ADMET properties of the three chemical compounds.

ADMET Properties									
Comp Id	**WS**	**IS %abs**	**Log Kp**	**LogBB**	**CNSP**	**CYP3A4**	**AMEST**	**ORAT**	**HT**
1019 for N-protein	-2.68	82.87	-2.47	-1.67	-3.99	yes	no	1.98	yes
1212 for M-protein	-4.59	72.87	-2.67	-1.77	-3.9	yes	no	2.21	yes
1992 for E-protein	-2.91	2.016	-2.73	-2.04	-5.69	no	no	2.55	no

CONCLUSION

The development of a SARS-Cov-2 vaccine is very important as it can enhance the immunity in the human host to tackle the infection. SARS-Cov-2 vaccine development is not an easy task due to the swift transmission of the virus among humans. Ran *et al*. [36] used the Auto Dock Vina tool to screen possible drugs by utilizing molecular docking with SARS-Cov-2 proteins. They studied luteolin (the main flavonoid in honeysuckle), ribavirin, remdesivir and chloroquine. Honeysuckle is usually supposed to have antiviral effects in traditional Chinese medicine. In their study, luteolin was originated to bind with a high affinity to the same sites of the main protease of SARS-Cov-2. Xiaopeng *et al*.

[37] used LeDock to determine the binding energy between SARS-Cov-2 proteins and contender molecules. Improvement analyses were used to demonstrate the possible pharmacological links of active molecules. The flavonoid rutin was recognized to fit comfortably into the M^{pro} substrate-binding pocket and showed a strong interaction with Toll-like receptors (TLR2, TLR6 and TLR7). Saadat *et al*. [38] used molecular docking technique to evaluate the binding affinities of 3699 drugs on the possible active sites of six proteins (Main protease, ADP Ribose phosphatase, Papain like protease, Spike protein, NSP-9 and NSP-10-16 complexes) of SARS-CoV-2. Their results of the top ligands (Theaflavin, Theasinensin A, Epigallocatechin and Favipiravir) exhibited the highest binding affinities against Main protease, ADP Ribose phosphatase, Papain like protease, Spike protein, NSP-9 and NSP-16 complexes, respectively. In another study conducted by Basu *et al*. [39], the authors selected five phytochemicals of flavonoid and anthraquinone subclasses as small molecules for the molecular docking study of S-protein of SARS-Cov-2 with its human receptor ACE2. They examined the binding sites on S-protein bound structure with its receptor and selected hesperidin, chrysin and emodin as competent natural products from both Chinese and Indian medicinal plants, to tackle SARS-Cov-2. The above studies have some limitations, such as they only focused on s-proteins and have exhibited lesser binding interactions and docking scores.

In this study, we performed molecular docking to screen potential inhibitors (2500 verified chemical compounds library) against SARS-Cov-2 N, M and E proteins in order to tackle COVID-19 pneumonia disease. Based on the lowest "S-score" and intermolecular binding interactions, we recognized compound id 1019 for N-protein with lowest "S-score" -11.5 and compound id 1212 for M-protein with lowest "S-score" -11.6 and compound id 1992 for E-protein with lowest "S-score" -10.3 with maximum hygrogen binding and intermolecular interactions. We took peptidomimetic Inhibitor N3 [35] as a reference drug with the lowest "S-score" -9.8 for our work. Our results show that all selected compounds after screening (1019, 1212 and 1992) outpaced peptidomimetic inhibitor N3. Moreover, by using Pyrx, we conducted re-docking and compared our results ranging between -10.3 to -10.6 on the basis of docking scores with those of the above studies [36-40] that have been found to be ranging between -9.6 to -10.0; our docking scores were found to be much higher compared to other studies.

This *in silico* knowledge will be helpful for the design of novel, safe (with fewer side effects, if the drug is administered *via* direct inhaling as compared to orally taken) and less expensive drugs to cure COVID-19 disease. We also hope that machine learning and computational intelligence methods could be applied to the drug discovery [12, 41-50].

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of this study are available within the article and its supplementary material.

FUNDING

This work has been supported by the National Natural Scientific Foundation of China (Nos. 61772119 and 31771471).

CONFLICT OF INTEREST

Dr. Wei Chen and Dr. Hao Lin are the Editorial Board Member of the Journal *Current Bioinformatics*.

ACKNOWLEDGEMENTS

Declared none.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

REFERENCES

[1] Jung SM, Akhmetzhanov AR, Hayashi K, *et al.* Real-time estimation of the risk of death from novel coronavirus (COVID-19) infection: inference using exported cases. J Clin Med 2020; 9(2): 523. http://dx.doi.org/10.3390/jcm9020523 PMID: 32075152

[2] Wu Y, Xie YL, Wang X. Longitudinal CT findings in COVID-19 pneumonia: Case presenting organizing pneumonia pattern. Radiology. Radiol Cardiothorac Imaging 2020; 2(1): e200031. http://dx.doi.org/10.1148/ryct.2020200031 PMID: 33778545

[3] Behzadi MA, Leyva-Grado VH. Overview of current therapeutics and novel candidates against influenza, respiratory syncytial virus and Middle East respiratory syndrome coronavirus infections. Front Microbiol 2019; 10: 1327. http://dx.doi.org/10.3389/fmicb.2019.01327 PMID: 31275265

[4] Stephenson N, Shane E, Chase J, *et al.* Survey of machine learning techniques in drug discovery. Curr Drug Metab 2019; 20(3): 185-93. http://dx.doi.org/10.2174/1389200219666180820112457 PMID: 30124147

[5] Su R, Liu X, Wei L, Zou Q. Deep-Resp-Forest: a deep forest model to predict anti-cancer drug response. Methods 2019; 166: 91-102. http://dx.doi.org/10.1016/j.ymeth.2019.02.009 PMID: 30772464

[6] Gallagher TM, Buchmeier MJ. Coronavirus spike proteins in viral entry and pathogenesis. Virology 2001; 279(2): 371-4. http://dx.doi.org/10.1006/viro.2000.0757 PMID: 11162792

[7] Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol 2020; 5(4): 562-9. http://dx.doi.org/10.1038/s41564-020-0688-y PMID: 32094589

[8] Wrapp D, Wang N, Corbett KS, *et al.* Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020; 367(6483): 1260-3. http://dx.doi.org/10.1126/science.abb2507 PMID: 32075877

[9] Prajapat M, Sarma P, Shekhar N, *et al.* Drug targets for corona virus: a systematic review. Indian J Pharmacol 2020; 52(1): 56-65. http://dx.doi.org/10.4103/ijp.IJP_115_20 PMID: 32201449

[10] Nazar H. Nanotechnology medicine-from gene delivery to tissue targeting. Pharm J 2013; 290: 115.

[11] Dao F-Y, Lv H, Yang Y-H, Zulfiqar H, Gao H, Lin H. Computational identification of N6-methyladenosine sites in multiple tissues of mammals. Comput Struct Biotechnol J 2020; 18: 1084-91. http://dx.doi.org/10.1016/j.csbj.2020.04.015 PMID: 32435427

[12] Zhang Z-M, Wang J-S, Zulfiqar H, Lv H, Dao FY, Lin H. Early diagnosis of pancreatic ductal adenocarcinoma by combining relative expression orderings with machine-learning method. Front Cell Dev Biol 2020; 8: 582864. http://dx.doi.org/10.3389/fcell.2020.582864 PMID: 33178697

[13] Ivashchenko A, Rakhmetullina A, Aisina D. How miRNAs can protect humans from coronaviruses COVID-19, SARS-CoV, and MERS-CoV. In: bioinformatics of genome regulation and structure/System biology (BGRS/SB-2020), pp. 445-446.

[14] Metsky HC, Freije CA, Kosoko-Thoroddsen T-SF, *et al.* CRISPR-based COVID-19 surveillance using a genomically-comprehensive machine learning approach. bioRxiv 2020. https://doi.org/10.1101/2020.02.26.967026

[15] Dao F-Y, Lv H, Zulfiqar H, *et al.* A computational platform to identify origins of replication sites in eukaryotes. Brief Bioinform 2021; 22(2): 1940-50. http://dx.doi.org/10.1093/bib/bbaa017 PMID: 32065211

[16] Fathima AJ, Murugaboopathi G, Selvam P. Pharmacophore mapping of ligand based virtual screening, molecular docking and molecular dynamic simulation studies for finding potent NS2B/NS3 Protease inhibitors as potential anti-dengue drug compounds. Curr Bioinform 2018; 13: 606-16. http://dx.doi.org/10.2174/1574893613666180118105659

[17] Zulfiqar H, Masoud MS, Yang H, *et al.* Screening of prospective plant compounds as H1R and CL1R inhibitors and its antiallergic efficacy through molecular docking approach. Computational Mathemat Methods Med 2021; ID 6683407. https://doi.org/10.1155/2021/6683407

[18] Bolton EE, Wang Y, Thiessen PA, *et al.* PubChem: integrated platform of small molecules and biological activities. Annual reports in computational chemistry. Elsevier 2008; pp. 217-41.

[19] Sterling T, Irwin JJ. ZINC 15–ligand discovery for everyone. J Chem Inf Model 2015; 55(11): 2324-37. http://dx.doi.org/10.1021/acs.jcim.5b00559 PMID: 26479676

[20] Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx.Chemical biology. Springer 2015; pp. 243-50.

[21] Mills N. Informatics for better science. Available from: www.cambridgesoft.com 2006.

[22] Tian W, Chen C, Lei X, Zhao J, Liang J. CASTp 3.0: Computed atlas of surface topography of proteins. Nucleic Acids Res 2018; 46(W1): W363-7. http://dx.doi.org/10.1093/nar/gky473 PMID: 29860391

[23] Studio D, Insight I. Accelrys Software Inc. San Diego, CA 2009; 92121.

[24] Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 2001; 46(1-3): 3-26. http://dx.doi.org/10.1016/S0169-409X(00)00129-0 PMID: 11259830

[25] Pires DE, Blundell TL, Ascher DB. pkCSM: predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. J Med Chem 2015; 58(9): 4066-72. http://dx.doi.org/10.1021/acs.jmedchem.5b00104 PMID: 25860834

[26] Ryan NJ, Lo JH. Delamanid: first global approval. Drugs 2014; 74(9): 1041-5. http://dx.doi.org/10.1007/s40265-014-0241-5 PMID: 24923253

[27] Stinson K, Kurepina N, Venter A, *et al.* MIC of delamanid (OPC-67683) against *Mycobacterium tuberculosis* clinical isolates and a proposed critical concentration. Antimicrob Agents Chemother 2016; 60(6): 3316-22. http://dx.doi.org/10.1128/AAC.03014-15 PMID: 26976868

[28] Li Y, Sun F, Zhang W. Bedaquiline and delamanid in the treatment of multidrug-resistant tuberculosis: Promising but challenging. Drug Dev Res 2019; 80(1): 98-105. http://dx.doi.org/10.1002/ddr.21498 PMID: 30548290

[29] Gler MT, Skripconoka V, Sanchez-Garavito E, *et al.* Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med 2012; 366(23): 2151-60. http://dx.doi.org/10.1056/NEJMoa1112433 PMID: 22670901

[30] Adkins JC, Brogden RN. Zafirlukast: a review of its pharmacology and therapeutic potential in the management of asthma. Drugs 1998; 55(1): 121-44. http://dx.doi.org/10.2165/00003495-199855010-00008 PMID: 9463793

[31] Dunn CJ, Goa KL. Zafirlukast: an update of its pharmacology and therapeutic efficacy in asthma. Drugs 2001; 61(2): 285-315. http://dx.doi.org/10.2165/00003495-200161020-00012 PMID: 11270943

[32] Virchow JC Jr, Prasse A, Naya I, Summerton L, Harris A. Zafirlukast improves asthma control in patients receiving high-dose inhaled corticosteroids. Am J Respir Crit Care Med 2000; 162(2 Pt 1): 578-85. http://dx.doi.org/10.1164/ajrccm.162.2.9905041 PMID: 10934090

[33] Wechsler ME, Garpestad E, Flier SR, *et al.* Pulmonary infiltrates, eosinophilia, and cardiomyopathy following corticosteroid withdrawal in patients with asthma receiving zafirlukast. JAMA 1998; 279(6): 455-7. http://dx.doi.org/10.1001/jama.279.6.455 PMID: 9466639

[34] Liu W, Zhou M, Li Z, *et al.* A selective small molecule DNA2 inhibitor for sensitization of human cancer cells to chemotherapy. EBioMedicine 2016; 6: 73-86. http://dx.doi.org/10.1016/j.ebiom.2016.02.043 PMID: 27211550

[35] Jin Z, Du X, Xu Y, *et al.* Structure-based drug design, virtual screening and high-throughput screening rapidly identify antiviral leads targeting COVID-19. bioRxiv 2020. https://doi.org/10.1101/2020.02.26.964882

[36] Yu R, Chen L, Lan R, Shen R, Li P. Computational screening of antagonists against the SARS-CoV-2 (COVID-19) coronavirus by molecular docking. Int J Antimicrob Agents 2020; 56(2): 106012. http://dx.doi.org/10.1016/j.ijantimicag.2020.106012 PMID: 32389723

[37] Hu X, Cai X, Song X, *et al.* Possible SARS-coronavirus 2 inhibitor revealed by simulated molecular docking to viral main protease and host toll-like receptor. Future Virol 2020; 15: 359-68. http://dx.doi.org/10.2217/fvl-2020-0099

[38] Saadat S, Mansoor S, Naqvi N, *et al.* Structure based drug discovery by virtual screening of 3699 compounds against the crystal structures of six key SARS-CoV-2 proteins. 2020; PPRID: PPR163865. http://dx.doi.org/10.21203/rs.3.rs-28113/v1

[39] Basu A, Sarkar A, Maulik U. Molecular docking study of potential phytochemicals and their effects on the complex of SARS-CoV2 spike protein and human ACE2. Sci Rep 2020; 10(1): 17699. http://dx.doi.org/10.1038/s41598-020-74715-4 PMID: 33077836

[40] Bhatia S, Giri S, Lal AF, *et al.* Identification of potential inhibitors of dietary polyphenols for SARS-CoV-2 M protease: an *in silico* study. Tropical Public Health 2020; 1: 21-9.

[41] Basith S, Manavalan B, Hwan Shin T, Lee G. Machine intelligence in peptide therapeutics: A next-generation tool for rapid disease screening. Med Res Rev 2020; 40(4): 1276-314. http://dx.doi.org/10.1002/med.21658 PMID: 31922268

[42] Basith S, Manavalan B, Shin TH, Lee G. SDM6A: a web-based integrative machine-learning framework for predicting 6mA sites in the rice genome. Mol Ther Nucleic Acids 2019; 18: 131-41. http://dx.doi.org/10.1016/j.omtn.2019.08.011 PMID: 31542696

[43] Hasan MM, Schaduangrat N, Basith S, Lee G, Shoombuatong W, Manavalan B. HLPpred-Fuse: improved and robust prediction of hemolytic peptide and its activity by fusing multiple feature representation. Bioinformatics 2020; 36(11): 3350-6. http://dx.doi.org/10.1093/bioinformatics/btaa160 PMID: 32145017

[44] Manavalan B, Basith S, Shin TH, Wei L, Lee G. Meta-4mCpred: A sequence-based meta-predictor for accurate DNA 4mC site prediction using effective feature representation. Mol Ther Nucleic Acids 2019; 16: 733-44. http://dx.doi.org/10.1016/j.omtn.2019.04.019 PMID: 31146255

[45] Manavalan B, Basith S, Shin TH, Wei L, Lee G. mAHTPred: a sequence-based meta-predictor for improving the prediction of anti-hypertensive peptides using effective feature representation. Bioinformatics 2019; 35(16): 2757-65.
http://dx.doi.org/10.1093/bioinformatics/bty1047 PMID: 30590410

[46] Cheng L. Computational and biological methods for gene therapy. Curr Gene Ther 2019; 19(4): 210.
http://dx.doi.org/10.2174/1566523219041910221133307
PMID: 31762421

[47] Feng YM. Gene therapy on the road. Curr Gene Ther 2019; 19(1): 6.
http://dx.doi.org/10.2174/1566523219999190426144513 PMID: 31190640

[48] Lv H, Dao F-Y, Zulfiqar H, *et al.* A sequence-based deep learning approach to predict CTCF-mediated chromatin loop. Brief Bioinform 2021; 22(5): bbab031.
http://dx.doi.org/10.1093/bib/bbab031 PMID: 33634313

[49] Zhang D, Chen H-D, Zulfiqar H, *et al.* iBLP: An XGBoost-Based Predictor for Identifying Bioluminescent Proteins. Comput Math Methods Med 2021; 2021: 6664362.
https://doi.org/10.1155/2021/6664362

[50] Yang H, Luo Y, Ren X, *et al.* Risk prediction of diabetes: Big data mining with fusion of multifarious physical examination indicators. Inf Fusion 2021.
http://dx.doi.org/10.1016/j.inffus.2021.02.015