Is Fostamatinib a possible drug for COVID-19? – A computational study

Sovan Saha^{1, +}, Anup Kumar Halder^{2, +}, Soumyendu Sekhar Bandyopadhyay², Piyali Chatterjee³, Mita Nasipuri², Debdas Bose⁴ and Subhadip Basu^{2,*}

¹Dr. Sudhir Chandra Sur Degree Engineering College, Computer Science and Engineering, Kolkata, 700074, India

²Jadavpur University, Computer Science and Engineering, Kolkata, 700032, India

³Netaji Subhash Engineering College, Computer Science and Engineering, Kolkata, 700152, India

⁴Institute of Hematology and Transfusion Medicine, Medical College Hospital, Kolkata, 700073, India

*subhadip.basu@jadavpuruniversity.in

⁺Equal Contribution, both shared 1st authorship

ABSTRACT

COVID-19 has turned out to be a global pandemic within a very short period since its first origin in China in December 2019. With the gradual increase in the mortality rate all over the world, there is an urgent need for an effectual drug. Though no clinically approved vaccine or drug is available until now but scientists are trying hard to identify potential antivirals to this new coronavirus. Several drugs like hydroxychloroquine, remdesivir, azithromycin etc. are put under evaluation in more than 300 clinical trials for the treatment of COVID-19. Few of them already show encouraging results. The main agent of disease progression of COVID-19 is SARS-CoV2/nCoV, which is believed to have ~89% genetic resemblance with SARS-CoV, a coronavirus responsible for the massive outbreak in 2003. With this hypothesis, a recently developed *in silico* Human-nCoV network and potential COVID-19 spreader proteins, have been derived from the Human-SARS-CoV protein interactions using SIS model and fuzzy thresholding, followed by a potential FDA drugs target based validation. We then perform a two-way analysis to identify the potential drug targets of COVID-19. In the first analysis, we identify the complete list of FDA drugs for the 37 level 1 and 4948 level 2 spreader proteins in this network followed by the application of a consensus strategy. In the second analysis, the same consensus strategy is applied but on a curated overlapping set of key genes identified from COVID-19 symptoms, risk factors and clinical outcome. The applied consensus strategy in both the analysis reveals that Fostamatinib, a FDA approved drug, has the highest drug consensus score both in level 1 and level 2. Further analysis reveals that Fostamatinib also targets CYP3A4, a level 2 spreader protein and the most common target for most of the potential COVID-19 drugs. A subsequent docking study also reveals that Fostamatinib has also the highest docking score with respect to 6LU7, the crystal structure of COVID-19 main protease in complex with an inhibitor N3, in comparison to other potential drugs like hydroxychloroquine, remdesivir, favipiravir and darunavir. Our computational study suggests that Fostamatinib may also be considered as one of the potential candidates for further clinical trials in pursuit to counter the spread of COVID-19.

Introduction

The world has witnessed several severe epidemics like Spanish flu, ebola, cholera etc. Now we are in the front of the most life threatening viral outburst with COVID-19. The feature which makes this new coronavirus, nCoV, unique is its quick ability to transmit through respiratory droplets on coming in direct contact or neighborhood of any infected COVID patient¹. It is considered to be one of the genera of Betacoronavirus which comes under the family of Coronaviridae. It is created by the assimilation of accessory, non-structural and structural proteins². According to the World Health Organization (WHO) coronavirus disease dashboard³, 3,679,499 confirmed cases of COVID-19, including 254,199 deaths have been reported as of 6:32pm CEST, 7 May 2020. Many treatments of antiviral drugs are considered and implemented to terminate COVID-19 based on the prior knowledge of major outbreaks of ebola, cholera etc. Moreover, along with these trial and error methods, an organized assessment of the drug chloroquine on nCoV has emerged⁴. But application of chloroquine on COVID-19 is contentious till date since these information have not been generated directly from the registered clinical trials in progress as reported by Zhang *et al*⁵.

Recently, a literature survey⁶ is implemented by a refined search in various online repositories to enfold various drug related COVID-19 research articles during the onset of this pandemic i.e. starting from January 1 and ending in March 25, 2020. Databases like Google Scholar, Science Direct, and PubMed etc. are marked as search strings for keywords like vaccine, anti-malaria drugs, treatment for COVID-19, traditional Chinese

Medicine for COVID-19, anti-viral drugs. Almost 22 articles⁶ have been filtered out based on the screening criteria as set by the computational search mechanism. In order to acquire a comparative idea about the recommended or suggested drugs till date for COVID-19, all the significant researches including these 22 articles have been extensively studied, the details of which have been listed in Table 1.

Table 1 List of significant research articles involving potential recommended drugs for COVID-19

SL. No.	Journal/Article name	Involved drugs	Report type	Drug Categorization	Results/Outcome
1	The Use of Anti-Inflammatory Drugs in the Treatment of People With Severe Coronavirus Disease 2019 (COVID-19): The Perspectives of Clinical Immunologists From China ⁷	Glucocorticoids	Clinical	Anti-malarial	Confirmation of the short-term efficacy of HCQ in the treatment of COVID-19
		IL-6 antagonist			
		JAK inhibitors			
		Chloroquine (CQ)/Hydroxychloroquine (HCQ)		Anti-inflammatory	
2	Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial ⁸	HCQ	Clinical	Anti-viral	Combination of the two is effective in the extermination of coronavirus.
		Azithromycin		Anti-inflammatory	
3	Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2) ⁹	Lianhuaqingwen (LH)	Laboratory test	Traditional Chinese Medicine	LH hinders the replication of SARS-COV-2
4	Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. ¹⁰	HCQ	<i>In vitro</i> Cytotoxicity and antiviral	Anti-malarial Anti-inflammatory	HCQ can effectively stop the infection of SARS-CoV-2 <i>in vitro</i> .
5	Aminoquinolines Against Coronavirus Disease 2019 (COVID-19): Chloroquine or Hydroxychloroquine ¹¹	HCQ	Opinion paper	Anti-malarial	Though both HCQ and CQ are beneficial but HCQ is more safer in comparison to CQ
		CQ			
		Other medicinal agents		Anti-viral	
6	Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study ¹²	Favipiravir (FPV)	Clinical	Anti-viral	FPV performs a faster clearance of viral infection with a better change in chest imaging.
7	TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Fedratinib ¹³	Janus kinase 2 (JAK2)	<i>In vitro</i> study	Anti-inflammatory	JAK2 inhibitor Fedratinib can prevent the deteriorating outcomes of TH17 associated cytokine storm in COVID-19.
		Fedratinib			
8	In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) ¹⁴	HCQ	<i>In vitro</i> study	Anti-malarial	Inhibits COVID-19.
		CQ			
9	Coronavirus Disease 2019 (COVID-19) Pneumonia in a Hemodialysis Patient ¹⁵	Lopinavir	Case study on Hemodialysis Patient	Anti-viral	Recovery symptoms noted though combination of the drugs needs more testing.
		Ritonavir			
10	Repurposing of clinically approved drugs for treatment of coronavirus disease 2019 in a 2019-	Cepharanthine	Cell culture and pangolin coronavirus	Anti-inflammatory	Reduction of cytopathic effects in cell culture.
		Selamectin		antineoplastic	

	novel coronavirus (2019-nCoV) related coronavirus model. ¹⁶	Mefloquine	modelling	anti-parasitic	
11	Traditional Chinese Medicine for COVID-19 Treatment ¹⁷	Qingfei paidu decoction	Case study	Traditional Chinese Medicine	Control COVID-19.
12	COVID-19: combining antiviral and anti-inflammatory treatments ¹⁸	Baricitinib Fedratinib Ruxolitinib	<i>In silico</i>	Anti-inflammatory	Favourable in COVID-19 treatment.
13	The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. ¹⁹	Remdesivir	<i>In vitro</i> study	Anti-viral	High effectiveness of remdesivir against RNA viruses in cell-based assays.
14	Virus against virus: a potential treatment for 2019-nCoV (SARS-CoV-2) and other RNA viruses. ²⁰	CRISPR/Cas13d strategy	<i>In vitro</i> test	Others treatment/drugs	Capable of RNA virus treatment
15	Therapeutic options for the 2019 novel coronavirus (2019-nCoV) ²	Remdesivir Umifenovir Oseltamivir ASC09F Other inhibitors	Opinion	Anti-viral	Biocontainment capability against covid-19.
16	Inhibitors of RAS Might Be a Good Choice for the Therapy of COVID-19 Pneumonia ²¹	Renin-Angiotensin System (RAS) inhibitors	Opinion	Others treatment/drugs	ACEI and AT1R inhibitors could be used in patients with COVID-19 pneumonia to reduce the pulmonary inflammatory response and mortality.
17	Case of the Index Patient Who Caused Tertiary Transmission of Coronavirus Disease 2019 in Korea: the Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Pneumonia Monitored by Quantitative RT-PCR. ²²	Lopinavir RitonavirA	Clinical	Anti-viral	Combat COVID-19 harmful effect.
18	Therapeutic strategies in an outbreak scenario to treat the novel coronavirus originating in Wuhan, China ²³	Angiotensin-converting enzyme 2	Opinion	Others treatment/drugs	Potentiality of ACE2-Fc to act as the neutralizing antibody which can be used for COVID-19 treatment.
19	Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. ²⁴	Remdesivir Ribavirin Penciclovir Nitazoxanide Nafamostat Remdesivir Favipiravir Chloroquine	<i>In vitro</i> study	Anti-viral Anti-malarial	Drugs proved to be effective with Remdesivir and chloroquine.
20	Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. ²⁵	Lopinavir/Ritonavir Arbidol Shufeng Jiedu	Case study	Anti-viral Anti-malarial	Effective treatment was observed.
21	First case of 2019 novel coronavirus in the United States. ²⁶	Remdesivir	Case Study on single patient	Anti-viral	Patient got recovered.
22	One highly suspected case of novel coronavirus	Traditional Chinese	Case Study on	Traditional Chinese Medicine	Patient got recovered.

	pneumonia treated by Integrated Traditional Chinese and Western medicine and nucleic acid analysis. ²⁷	Medicine	single patient		
23	COVID-19 in patients with HIV: clinical case series ²⁸	Darunavir	Case Study on single patient	Anti-viral	Darunavir was proved to be ineffective against COVID-19 due to low affinity.
24	Favipiravir: Pharmacokinetics and Concerns About Clinical Trials for 2019-nCoV Infection	Favipiravir	Opinion	Anti-viral	Recommendation for use in COVID-19. Needs more clinical confirmation.
25	Remdesivir for COVID-19 : challenges of underpowered studies ²⁹	Remdesivir	Case study	Anti-viral	Effective against COVID-19.

It can be observed from Table 1, that the most recommended drugs are like hydroxychloroquine, azithromycin, lopinavir, ritonavir, remdesivir, and favipiravir. It also signifies that the amount of data accessible for these drugs is insufficient to recommend any one of them as a treatment for COVID-19 until and unless necessary amount of appropriate clinical trials are executed. Relative data comparison is missing in almost all human related studies about COVID-19. So it is uncertain that whether the COVID infected patient actually recovers due to the application of the suggested drug or he/she recovers due to the given clinical extensive care and isolation. However, some of the *in vitro* studies have shown favourable results but these are all preliminary data, which need much more evidence before putting it in clinical trials.

But due to daily increase in the number of deaths³, there is an urgent need for the identification of a potential vaccine/drug which will eventually eradicate COVID-19. So, with no other alternatives left, clinical trials has been started by WHO³⁰ on all the suggested drugs till date including the ones as mentioned in Table 1, which are somehow proved to be substantially beneficial on case studies of COVID-19.

Drug design needs proper understanding of disease transmission mechanism which can be effectively done through the analysis of Host-pathogen protein-protein interaction networks (PPIN)³¹. Pathogen is detrimental in disease progression as it has the potential to transform itself by mutation. Infection of pathogen gets broadcasted through the connecting edge or interaction between host and pathogen. Thus, proper exploration of target proteins and its interactions in Host-pathogen protein-protein interaction³² networks is essential for potential drug discovery. However, there is no approved Human-nCoV PPIN till date. So, this motivates us to develop a Human-nCoV PPIN through SIS model³³ and fuzzy thresholding. Further study of protein targets of potential Food and Drug Administration (FDA) drugs³⁴ of COVID-19 in our network shows that FDA approved drug, Fostamatinib³⁵, can be a potential drug for COVID-19 treatment. Rigel Pharmaceuticals, Inc. got approval for TAVALISSE (fostamatinib disodium hexahydrate) for the treatment of Chronic Immune Thrombocytopenia³⁶ from FDA on 17/04/2018. The key points which are associated with this research work can be highlighted as:

- Recently we have developed an *in silico* model to identify potential spreader proteins in a Human-nCoV interaction network^{37,38}.
- The developed model was validated using the target proteins of the potential FDA drugs³⁴ for COVID-19 treatment.
- A two-way analysis: 1) Human-nCoV interaction network analysis 2) COVID-19 symptoms, risk factors and clinical outcome based analysis have been implemented to detect the potential candidate FDA drugs for COVID-19.
- In the first analysis, spreader proteins in a Human-nCoV interaction network are analyzed using available DrugBank data^{39,40}. Potential FDA drugs having these spreader proteins as known targets are identified. A consensus strategy has been employed to rank the drugs having the highest overlap of target proteins with respect to the level-1 and level-2 spreader nodes in the Human-nCoV interaction network.
- In the second analysis, various human genes associated with COVID-19 symptoms⁴¹, risk factors⁴¹ and clinical outcome⁴¹ are detected using disease-gene dataset fetched from DisGeNET⁴². These multiple gene sets are

compared with each other using molbiotools⁴³. The resultant gene set is overlapped with curated dataset of COVID-19 (under category respiratory tract disease & viral disease) released from the Comparative Toxicogenomics Database (CTD)⁴⁴ to find the most common overlapping gene set associated with COVID-19. The most active top 10 key genes from this set are identified at each of level-1 and level-2 in our Human-nCoV interaction network based on the sorting of fuzzy (level-1) and spreadability index score (level-2) in descending order. These key genes/spreader proteins are analyzed using available DrugBank data^{39,40}. Potential FDA drugs having these spreader proteins as known targets are identified. Then the same consensus strategy, as in first analysis, has been applied.

- In both the analysis, Fostamatinib³⁵, an FDA approved drug and commonly used for the treatment of chronic immune thrombocytopenia (ITP)⁴⁵, ranks as the top having most overlap of target proteins in both the level-1 and level-2 networks
- Further analysis reveals that Fostamatinib also targets CAYP34A^{46,47}, a common target for almost all the FDA approved drugs³⁴ for COVID-19.
- Fostamatinib is used for thrombocytopenia⁴⁶ which is also associated with severe coronavirus disease 2019 (COVID-19) infections⁴⁸.
- Fostamatinib also generates the highest docking score with 6LU7⁴⁹ (the crystal structure of COVID-19 main protease in complex with an inhibitor N3) among the other potential FDA drugs³⁴.

Dataset

Our proposed methodology involves 4 datasets: 1) Human PPIN^{50,51} 2) SARS-CoV PPIN⁵² 3) SARS-CoV-Human PPIN⁵² and 4) SARS-CoV2 proteins⁵³. The overall dataset statistics is highlighted in Table 2.

Table 2 Description and details of the datasets

Database Name	Description	Nodes	Interactions/Edges
Human PPIN	Human-human protein interactions	21557	342353
SARS-CoV PPIN	SARS-CoV-SARS-CoV protein interactions	7	----
SARS-CoV-Human PPIN	SARS-CoV-Human protein interactions	120	118
SARS-CoV2 proteins	UniProt collected reviewed COVID19 proteins	14	----

Figure 1 Formation of SARS-CoV-Human and COVID19-Human PPIN. Blue nodes represent SARS-CoV spreaders while yellow and green denotes level 1 and level 2 human spreaders respectively in SARS-CoV-

Human PPIN. In SARS-CoV2-Human PPIN red nodes denotes SARS-CoV2 spreaders while yellow and green hold the same meaning as that of SARS-CoV-Human PPIN.

Methods

The entire working mechanism for identifying Fostamatinib as one of the potential drug for COVID19 treatment can be categorized in 4 major sections: 1) detection of spreader nodes³⁷ in Human-nCoV PPIN 2) identification of potential FDA approved drugs with respect to COVID19 spreader nodes using Human-nCoV interaction network analysis 3) identification of potential candidate FDA drugs with respect to COVID-19 spreader nodes using COVID-19 symptoms, risk factors and clinical outcome based analysis 4) computational docking of potential drugs with respect to COVID19 protein structures.

Detection of spreader nodes in Human-nCoV PPIN

No clinically approved PPIN of Human-nCoV is available till date. So, an attempt has been made to construct a Human-nCoV PPIN based on the available PPIN information of SARS-CoV which have ~89% similarity^{54,55} with SARS-CoV2. Not every protein in a PPIN is a spreader protein/node. Spreader proteins are considered to be those specific proteins which have unique fast capability of transmitting infection in its neighbourhood in a short period of time³⁷. They are identified through spreadability index computed by the combination of three terminologies: 1) Edge ratio⁵⁶ 2) Neighbourhood density⁵⁶ and 3) node weight⁵⁷. Proteins having high spreadability index are spreader proteins. Identification of spreader proteins is conducted initially in SARS-CoV PPIN dataset. Corresponding connected human proteins i.e. level 1 and level 2 of selected SARS-CoV spreader proteins are selected from SARS-CoV-Human PPIN and Human PPIN dataset respectively. Hence, spreader proteins in level 1 and level 2 human proteins of SARS-CoV are detected by spreadability index. The selected spreader nodes are also validated by Susceptible-Infected-Susceptible (SIS) model³³ (see Figure 1). This results in the formation of a PPIN which consists of 7 SARS-CoV, 24 level 1 and 111 level 2 human spreader proteins respectively under low threshold³⁷. The potential Human-nCoV interactions have been identified using developed in silico fuzzy PPI model⁵⁸. In this model, SARS-COV spreader (level-1 and level-2) proteins in human are considered as the candidate set of interactors for nCoV³⁸. The nCoV-Human pair-wise relationships are quantified using the semantic similarity of their annotated GO pairs. A hybrid approach has been applied to assess the semantic similarity between any GO target pairs using the topological properties of three GO sub graphs (BP: Biological Process, MF: Molecular Function and CC: Cellular Component)⁵⁹. These GO-level assessment scores are incorporated to obtain the fuzzy interaction affinity (score ranges [0, 1]) between the target Human and nCoV protein pair and results (see Figure 1). The high specificity (99.9%) has been achieved on a threshold of 0.4 fuzzy interaction affinity score on a benchmark Human PPI dataset. Finally, with the high specificity threshold, potential interactions are identified between nCoV bait and human prey³⁸.

Figure 2 Consensus approach adopted to choose Fostamatinib as a potential COVID19 drug. Other connecting biological links for choosing the same have been also highlighted.

Algorithm-1: Potential Drug Selection using Consensus Strategy (PDS_CS)**Input:** The set of spreader proteins in COVID19-human PPIN, as $S^l = \{S_1, S_2, \dots, S_n\}$ The set of drugs listed in *DrugBank*, $D^l = \{D_1, D_2, \dots, D_n\}$ for spreader protein S^i , ($1 \leq i \leq n$).**Output:** *mxKey*- a potential drug for *COVID19*

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 $DL^1 \leftarrow [], DL^2 \leftarrow [],$       # Empty list of drug for level-1 and level-2 spreader
 $Dc^1 \leftarrow \{\}, Dc^2 \leftarrow \{\}$     # Empty dictionary for drug consensus score (DCS) for drugs
for each spreader protein  $S^i$  from  $S^{l=1}$  do
    if  $S^i \in D_t(D_k)$  then
        append  $D_k$  in  $DL^1$ 
    End if
End for
for each drug  $D_i$  from  $DL^1$  do
    compute  $DCS^1(D_i)$  and
     $Dc^1[D_i] \leftarrow DCS^1(D_i)$ 
End for
for each spreader protein  $S^i$  from  $S^{l=2}$  do
    if  $S^i \in D_t(D_k)$  then
        append  $D_k$  in  $DL^2$ 
    End if
End for
for each drug  $D_i$  from  $DL^2$  do
    compute  $DCS^2(D_i)$  and
     $Dc^2[D_i] \leftarrow DCS^2(D_i)$ 
End for
 $Dc_{sort}^1 \leftarrow sort_{desc}(Dc^1)$ 
 $Dc_{sort}^2 \leftarrow sort_{desc}(Dc^2)$ 
if  $Dc_{sort}^1(D_0^1) > Dc_{sort}^2(D_0^2)$  then
     $mxKey \leftarrow D_0^1$       # drug  $D$  from  $Dc^1$  with highest  $DCS^1$  value in  $DL^1$ 
else
     $mxKey \leftarrow D_0^2$       # drug  $D$  from  $Dc^1$  with highest  $DCS^2$  value in  $DL^1$ 
return  $mxKey$ 

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 $D_t(D_k)$: Target proteins of drug D_k $DCS^t(D_i)$: Drug Consensus Score of drug D_i at level t $sort_{desc}(Dc^f)$: Descending ordered sorting of dictionary Dc^f , based on the values of the dictionary.
 f -level of spreader protein.

Identification of potential candidate FDA drugs with respect to COVID-19 spreader nodes using Human-nCoV interaction network analysis

Once the COVID19-human PPIN is formed, all the level 1 and level 2 human proteins of COVID19 are mapped with their corresponding drugs from DrugBank³⁹. DrugBank is an online repository⁴⁰ which contains comprehensive data about drugs, drug protein targets and information about drug metabolism. Due to the high quality annotation in DrugBank, it becomes the mostly used databases in almost all *in silico* methodologies which are involved in drug design, docking of drugs and drug interaction prediction. It contains near about 60% and 10% of FDA approved and experimental drugs respectively³⁹. On proper analysis, it has been observed that various spreader nodes in COVID19-human PPIN are the protein targets of potential COVID19 FDA listed drugs³⁴: hydroxychloroquine^{8,60}, azithromycin⁸, lopinavir⁶¹, ritonavir⁶², remdesivir^{63–65}, and favipiravir^{66,67}. The details of significant number of overlap between spreader nodes and drug protein targets are highlighted in Table 3³⁸. It can be observed from Table 3, that hydroxychloroquine has the highest hit/overlap i.e. 4 while each of azithromycin, lopinavir, ritonavir and darunavir has 2 hits³⁸. Remdesivir and favipiravir has one hit individually³⁸. Remdesivir is the only drug that acts directly on COVID19 protein R1AB_SARS2.

Table 3 Details of overlap of spreader nodes and potential COVID19 FDA listed drugs

Sl. No.	COVID19 FDA listed Drugs	DrugBank ID	Drug Protein targets/ Spreader nodes	No. of hits
1	Hydroxychloroquine	DB01611	TLR9, ACE2, CYP3A4, ABCB1	4
2	Azithromycin	DB00207	CYP3A4, ABCB1	2
3	Lopinavir	DB01601	CYP3A4, ABCB1	2
4	Ritonavir	DB00503	CYP3A4, ABCB1	2
5	Remdesivir	DB14761	R1AB_SARS2	1
6	Favipiravir	DB12466	ABCB1	1
7	Darunavir	DB01264	CYP3A4, ABCB1	2

Significant overlapping results of drug targets and spreader nodes in Table 3 motivates us to do further analysis and to develop a consensus strategy to identify a potential drug for COVID19 treatment. The consensus strategy is described in Algorithm 1 (PDS_CS). Drug consensus score (DCS) is used in PDS_CS which is defined as the frequency of occurrences of a drug at a particular level of PPIN. Execution of PDS_CS algorithm is also highlighted in Figure 2 by considering a sample random COVID19-Human PPIN.

Identification of potential candidate FDA drugs with respect to COVID-19 spreader nodes using COVID-19 symptoms, risk factors and clinical outcome based analysis

COVID-19 is associated with certain health symptoms like cough, fever, breathing difficulty etc. These symptoms are linked with specific human gene sets which are chosen as the possible targets (preys) by the bait i.e. nCoV. The same is also true for other risk factors, clinical outcomes of COVID-19. So, all these genes under the mentioned categorization are grouped together⁴¹ from the disease-gene dataset which is available from DisGeNET. DisGeNET⁴² is considered to be one of the major resources which cover all the relevant information about various diseases. These multiple gene sets are compared with each other⁴¹ using molbiotools⁴³. The resultant gene set is then again compared⁴¹ with curated COVID-19 dataset available in Comparative Toxicogenomics Database (CTD)⁴⁴ under the category of respiratory tract disease & viral disease to obtain an overlapping gene set. CTD⁴⁴ is yet another significant resource which collects, organizes and stores scientific data which describes the interrelationship between proteins, pathways, interactions, drugs etc. The overlapping gene set is further intersected with the spreader protein set in level-1 and level-2 of our generated Human-nCoV interaction network³⁸. Top 10 key genes are selected from the resultant intersection in each of both the levels based on the fuzzy score and spreadability index score in score in level-1 and level-2 respectively. These genes are considered to be the most significant genes which play an important role in COVID-19 transmission^{68–72} as well as in its prevention^{73–77} in Human-nCoV interaction network. Potential FDA drugs having these key genes/spreader proteins as known targets are identified from DrugBank data^{39,40}. Then PDS_CS algorithm is executed to identify the most potential candidate FDA drug for COVID19.

Computational molecular docking of potential drugs with respect to 6LU7, the crystal structure of COVID-19 main protease

One of the most powerful approaches for structure based drug discovery is molecular docking. It is defined as the analysis of how well more than one molecular structures (drug and protein or enzyme) get attached with each other⁷⁸. In other word, docking can be interpreted as molecular modeling methodology, which is implemented to anticipate how small molecules i.e. ligands interrelate with protein i.e. enzyme. Jin *et al*⁴⁹ detected N3, which is defined as a mechanism-based inhibitor. The detection is executed by computer-aided drug design. Subsequently, they also identified the crystal structure⁴⁹ of COVID-19 virus M^{Pro} in complex with this compound. It is enlisted with id: 6LU7 in Protein Data Bank (PDB)⁷⁹. Protein-ligand docking is executed by using Molegro Virtual Docker (version: 6.0) between potential COVID19 FDA listed drugs and 6LU7 to measure the effectiveness of the drug on COVID19. Identification of potential binding site is done by using grid based cavity prediction. Blind docking is chosen due to the absence of active ligand in the predicted cavity. Flexible ligand models are used. Ligands are oriented differently and energy scores are the basis of ranking. For each ligand, the entire algorithm is set at 1500 iterations with a simplex evolution size of 10 runs. Compounds which require lowest energy to bind are considered to be the best. The molecules of the potential COVID19 FDA listed drugs are downloaded from DrugBank³⁹ in Structure data file (SDF) format (3D conformer). The docking returns two types of scores: 1) Moldock scores and 2) Rerank scores. These scores assist in the identification of the best molecules docked in the selected target site. All the molecules are sorted based on these scores which represent the lowest energy required to get tied up with amino acid (AA) components.

Figure 3 Application of PDS_CS algorithm in Human-CoV PPIN (level 1). DCS score of Fostamatinib in level 1 is 7 (green nodes). Blue and yellow nodes denote COVID19 and other level 1 proteins respectively.

Results

Computational study and results of associated drugs with human proteins in Human-nCoV PPIN shows that there is a probability that Fostamatinib may act as one of the potential candidates for COVID-19 treatment.

Drug-consensus results for COVID-19 spreader nodes using Human-nCoV interaction network analysis

Drugs along with their corresponding drug id are mapped with all level 1 and level 2 human spreader proteins of COVID19 by matching the corresponding drug protein targets with spreader nodes. It is observed after applying PDS_CS algorithm that Fostamatinib has a significant overlap of 155 target proteins in our Human-nCoV PPIN

which is also the highest frequency of occurrence in the entire PPIN when compared to the remaining human protein associated drugs (i.e. highest DCS score as described earlier in methodology section). It has a DCS score of 7 (see Figure 3 and Table 4) and 148 (see Figure 4 and Table 5) in level 1 and level 2 human spreader proteins respectively.

Table 4 Detailed analysis of DCS score at level 1 (Top 5 DCS have been shown)

Drug	Drug ID	DCS (Level 1)
Fostamatinib	DB12010	7
Arsenic trioxide	DB01169	2
Acetylsalicylic acid	DB00945	2
Resveratrol	DB02709	2
Tamoxifen	DB00675	1

Figure 4 Application of PDS_CS algorithm in Human-CoV PPIN (level 2). DCS score of Fostamatinib in level 2 is 148 (green nodes). Blue and yellow nodes denote COVID19 and other level 1 spreader proteins respectively. Other level 2 spreaders are not shown to avoid visual complexity.

Table 5 Detailed analysis of DCS score at level 2 (Top 5 DCS have been shown)

Drug	Drug ID	DCS (Level 2)
Fostamatinib	DB12010	148
Copper	DB09130	88
Zinc acetate	DB14487	57
Zinc	DB01593	57
Zinc chloride	DB14533	57

Drug-consensus results for COVID-19 spreader nodes using COVID-19 symptoms, risk factors and clinical outcome based analysis

Grouping of genes based on various categorizations of COVID-19 symptoms, risk factors and clinical outcome is done using DisGeNET⁴². The numerical statistics of the result is highlighted in Table 6. Molbiotools is used to compare these gene sets to obtain a gene set containing 4931 unique genes. These genes are further compared with curated COVID-19 dataset of CTD⁴⁴ which contains 12672 genes. The comparison generates an overlapping gene set containing 3525 genes. These genes when used for validation against our spreader proteins

in Human-nCoV interaction network³⁸, produces a significant overlap of 1448 genes in both level-1 and level-2. This highlights the fact that 1448 out of 3525 genes are selected as spreader nodes in our network. Hence top 10 key genes are selected from 1448 genes in each of both the levels based on the fuzzy score and spreadability index score in score in level-1 and level-2 respectively. The selected top genes from level-1 are PPIA, ACE2, EIF3F, UBC, PRKDC, CDK2, CDK1, AKT1, PRKCA and TRAF6 while the selected top genes from level-2 are APP, ELAVL1, NTRK1, XPO1, MEOX2, GRB2, EGFR, TP53, BAG3 and NXF1. Potential FDA drugs having these key genes/spreader proteins as known targets are identified from DrugBank data^{39,40} (see Table 7 and Table 8). It is also observed after applying PDS_CS algorithm on the obtained result in Table 7 and Table 8 that Fostamatinib has a significant overlap of 3 target proteins which is also the highest frequency of occurrence.

Table 6 Statistical analysis of genes in COVID-19 symptoms, risk factors and clinical outcome

Categorizations	Symptoms	Total no. of genes
COVID-19 symptoms ⁴¹	Cough	270
	Fever	1743
	Dyspnea	323
	Pneumonia	1416
Risk factors ⁴¹	Heart Disease	1964
	Kidney Disease	2131
	Lung Disease	1018
	Diabetes	5078
	Hypertension	1573
	Cancer	4747
Clinical Outcomes (Mild & Moderate Case) ⁴¹	Lymphopenia	241
	Pulmonary infiltrate	43
Clinical Outcomes (Severe Case) ⁴¹	Leukocytosis	179
	Neutrophilia	152
	Sepsis	1506
	Kidney injury	228
	Coagulopathy	21
	Thrombocytopenia	774
	Multiple organ failure	25

Table 7 Mapping of FDA drug of DrugBank with selected key genes of level-1

Level-1 Key Genes	Approved/Approved & Investigational Drug	
	Drug	Drug ID
PPIA	Cyclosporine	DB00091
	Copper	DB09130
ACE2	Hydroxychloroquine	DB01611
	Chloroquine	DB00608
EIF3F	No approved drug	
UBC	No approved drug	
PRKDC	Caffeine	DB00201
CDK2	Bosutinib	DB06616
CDK1	Fostamatinib	DB12010
PRKCA	D-alpha-Tocopherol acetate	DB14002
	Midostaurin	DB06595
	alpha-Tocopherol succinate	DB14001
	Phosphatidyl serine	DB00144
	Vitamin E	DB00163
	Tamoxifen	DB00675
AKT1	Ingenol mebutate	DB05013
	Arsenic trioxide	DB01169
TRAF6	No approved drug	

Table 8 Mapping of FDA drug of DrugBank with selected key genes of level-2

Level-2 Key Genes	Approved/Approved & Investigational Drug	
	Drug	Drug ID
APP	Aluminium phosphate	DB14517
	Dimercaprol	DB06782
	Copper	DB09130
	Florbetapir (18F)	DB09149
	Flutemetamol (18F)	DB09151
	Deferoxamine	DB00746
	Zinc	DB01593
	Zinc sulfate, unspecified form	DB14548
	Florbetaben (18F)	DB09148
	Zinc acetate	DB14487
	Aluminum acetate	DB14518
	Aluminium	DB01370
	Zinc chloride	DB14533
ELAVL1	No approved drug	
NTRK1	Entrectinib	DB11986
	<i>Fostamatinib</i>	<i>DB12010</i>
	Cenegermin	DB13926
	Amitriptyline	DB00321
	Imatinib	DB00619
	Regorafenib	DB08896
	Larotrectinib	DB14723
XPO1	Selinexor	DB11942
MEOX2	No approved drug	
GRB2	Pegademase	DB00061
EGFR	Lidocaine	DB00281
	Gefitinib	DB00317
	<i>Fostamatinib</i>	<i>DB12010</i>
	Zanubrutinib	DB15035
	Cetuximab	DB00002
	Erlotinib	DB00530
	Vandetanib	DB05294
	Osimertinib	DB09330
	Dacomitinib	DB11963
	Brigatinib	DB12267
	Foreskin keratinocyte (neonatal)	DB10772
	Trastuzumab	DB00072
	Lapatinib	DB01259
	Panitumumab	DB01269
	Afatinib	DB08916
	Necitumumab	DB09559
	Neratinib	DB11828
TP53	Zinc acetate	DB14487
	Zinc chloride	DB14533
	Acetylsalicylic acid	DB00945
	Zinc	DB01593
	Zinc sulfate, unspecified form	DB14548
BAG3	No approved drug	
NXF1	No approved drug	

Docking results for potential COVID-19 drugs with respect to 6LU7

Molecular docking is used in the proposed methodology to measure the binding capability of the potential COVID19 drugs on 6LU7, the crystal structure of COVID-19 main protease. The detailed procedure of execution has been already discussed in methodology section. In this work, SDF format (3D conformer) is used for the docking of all the COVID19 drugs. All the results of docking are highlighted in Table 9. It can be observed from Table 9, that Fostamatinib shows high binding affinity scores in comparison to remdesivir,

hydroxychloroquine, favipiravir, darunavir, azithromycin, lopinavir and ritonavir. Docking has been also performed between 6LU7 and the mapped FDA drugs of key genes in level-1 and level-2 (see Table 7 and Table 8), the result of which has been shown in Table 10. It also proves the fact that Fostamatinib has the highest docking score.

Docking results for active metabolites/promoiety of COVID-19 Prodrugs with respect to 6LU7

Several drug molecules consist of pharmacologically inactive compounds which are known as Prodrugs⁸⁰. These drugs get metabolized after entering in human body to liberate the active drug. On careful observation, it has been noted that Fostamatinib is also a prodrug. Fostamatinib (R788) is considered to be an orally induced prodrug in human which releases active metabolite/promoiety R940406 (R406)⁸¹. R406 is a spleen tyrosine kinase (SYK) inhibitor, which is responsible for the treatment of rheumatoid arthritis⁸¹. Similar instances have been also observed in the case of remdesivir and favipiravir. So the binding capability of these active metabolites/promoiety also needs to be validated against 6LU7 by molecular docking for consideration of any prodrug as a COVID19 drug. The results of this docking are depicted in Table 11. It can be inferred from Table 11 that R406 also shows high binding affinity scores in comparison to the others which in turn promotes the fact that Fostamatinib can be a potential COVID19 drug. Molecular docking results of Fostamatinib and its corresponding promoiety, R406 have been also highlighted in Figure 5.

Figure 5 Molecular docking results of prodrug Fostamatinib and its corresponding promoiety, R406. Fostamatinib and R406 both have high binding affinity scores in comparison to the other potential COVID19 drugs.

Table 9 Best dock poses for potential COVID19 drugs and interactions of hydrogen bonds with respect to 6LU7

Drugs	Drug ID	Moldock score	Rerank Score	Best docked poses	H-bond interaction details best pose	H-bond interaction best pose
Fostamatinib	DB12010	-140.495	-102.464
Remdesivir	DB14761	-134.19	-56.312
Hydroxychloroquine	DB01611	-106.266	-69.417

Favipiravir	DB12466	-62.855	-55.371
Darunavir	DB01264	-128.798	-80.316
Azithromycin	DB00207	-86.77	29.53

Lopinavir	DB01601	-83.09	-30.19
Ritonavir	DB00503	-110.36	103.40

Table 10 Docking scores between 6LU7 and the mapped FDA drugs of key genes in level-1 and level-2

Drug	Drug ID	Moldock Score	Rerank Score
Fostamatinib	DB12010	-140.495	-102.464
Larotrectinib	DB14723	-140.477	-96.833
Selinexor	DB11942	-137.622	-95.531
Regorafenib	DB08896	-136.333	-87.952
Lapatinib	DB01259	-132.411	-77.797
Osimertinib	DB09330	-128.307	-71.159
Bosutinib	DB06616	-128.113	-31.981
Imatinib	DB00619	-126.843	-36.034
Gefitinib	DB00317	-126.808	-87.68
Neratinib	DB11828	-125.872	-73.871
Afatinib	DB08916	-125.727	-31.114
Cyclosporine	DB00091	-119.025	-4.147
Vandetanib	DB05294	-117.197	-76.946
Dacomitinib	DB11963	-116.462	73.271
Zanubrutinib	DB15035	-115.673	-72.988
Erlotinib	DB00530	-113.65	77.383
Florbetaben (18F)	DB09148	-111.68	-75.998
Deferoxamine	DB00746	-111.072	0.394
Florbetapir (18F)	DB09149	-108.564	-81.287
Entrectinib	DB11986	-91.681	346.912
Flutemetamol (18F)	DB15058	-85.347	-70.097
Brigatinib	DB12267	-80.187	271.203
Amitriptyline	DB00321	-75.386	-96.042
Lidocaine	DB00281	-65.781	-34.584
Caffeine	DB00201	-60.617	-55.691
Dimercaprol	DB06782	-46.439	-39.003
Copper	DB09130	-28.861	-27.328
Midostaurin	DB06595	-86.346	-48.092
Tamoxifen	DB00675	-123.549	-84.857

Table 11 Best dock poses for active metabolites/promoieties of potential COVID-19 prodrugs with respect to 6LU7

Prodrugs	Drug id	Active promoieties	Moldock Score	Rerank Score	Best docked poses	H-bond interaction details best pose	H-bond interaction best pose
Fostamatinib	DB12010	R406 (using 3FQS ^{82,83})	-110.11	-93.83
Remdesivir	DB14761	GS-441524	-93.37	-76.07
Favipiravir	DB12466	RdRp complex (6K32 ^{84,85})	-50.72	-45.20

Analysis of 3 key target genes of Fostamatinib identified in level-1 and level-2 of Human-nCoV interaction network in COVID-19 symptoms, risk factors and clinical outcome based analysis

The three key target genes of Fostamatinib as identified in Table 7 and Table 8, are CDK1 (level-1) and NTRK1, EGFR (level-2). On careful observation, it has been noted that these three genes are related to the most significant COVID-19 symptoms, risk factors and clinical outcomes which are highlighted in Table 12. Moreover, these 3 genes also play an important role in response to the viral infections (see Table 13). All these depict the fact that Fostamatinib might be a potential drug treatment to COVID-19 treatment.

Table 12 Mapping of CDK1 and NTRK1, EGFR with COVID-19 symptoms, risk factors and clinical outcomes

Drug	Key Target Genes	Level	COVID-19 symptoms	Clinical outcome (severe case)	Risk Factor
Fostamatinib	CDK1	Level-1	pneumonia	--	diabetes
					cancer
	NTRK1	Level-2	fever	--	kidney disease
					cancer
			pneumonia		hypertension
					lung disease
	EGFR	Level-2	pneumonia	neutrophilia	diabetes
					heart disease
			dyspnea		hypertension
					cancer
			fever	kidney injury	kidney disease
			cough	thrombocvtopenia	lung disease
			diabetes		

Table 13 Role of CDK1 and NTRK1, EGFR in viral infections

Drug	Key Target Genes	Level	Role in viral infections
Fostamatinib	CDK1	Level-1	Viruses have the capability to express some onco-proteins. These proteins could interfere with CDK and CIKs function, along with the induction of some signals which will lead to the replication of their genome inside the cells of the hosts ⁸⁶ .
	NTRK1	Level-2	NTRK1 has an active role in defence response ⁸⁷ to: 1. Neutrophil mediated immunity against viral infection ⁸⁷ . 2. Inflammatory response to wounding ⁸⁷ . 3. Bacterium ⁸⁷ .
	EGFR	Level-2	Inhibition of EGFR signalling might lead to the prevention of an excessive fibrotic response to SARS-CoV and other respiratory viral infections. ⁷⁷

Other significant studies

Drug interactions of genes have been also significantly studied and two online resources: STITCH^{88,89} and DGIdb⁹⁰ are used to fetch the corresponding interactive drugs/chemicals of the selected top key genes (as shown in Table 7 and Table 8) in level-1 and level-2 of Human-nCoV interaction network (see Table 14 and Table 15). In STITCH, top 10 drug interactions having high threshold (greater than 0.9) have been shown while in DGIdb, top 10 drug interactions having high interaction scores have been highlighted. It is to be noted here that the drugs like cyclosporine etc. involved in the interaction of these key genes should be also considered for COVID-19 treatment since these genes are found to play an active role in COVID-19 transmission⁶⁸⁻⁷² as well as in its prevention⁷³⁻⁷⁷.

Table 14 Level 1 key gene-drug interaction analysis

Level-1 Key Genes	STITCH ^{88,89}		DGIdb ⁹⁰		
	FDA approved Drug/chemical	Network interaction score (>0.9)	FDA approved Drug	Interaction Type	Score
PPIA	cyclosporine	0.984	cyclosporine	inhibitor, modulator	11
	calcium ions	0.980			
	fe(iii)	0.979			
	zn(ii)	0.979			
	3h-proline	0.976			
ACE2	losartan	0.990	lisinopril	inhibitor	6
	captopril	0.989	flutamide	N/A	1
	lisinopril	0.990			
	enalaprilat	0.983			
	mln-4760	0.982			
	angiotensin-(1-7	0.980			
	chloride	0.979			
CDK2	roscovitine	0.997	paclitaxel	N/A	2
	staurosporine	0.997	daunorubicin	N/A	2
	MgATP	0.991	lovastatin	N/A	2
	phosphate	0.986	eribulin	N/A	2
			hydrogen peroxide	N/A	2
			acetaminophen	N/A	2
			bosutinib	inhibitor	2
			raltitrexed	N/A	2
			dexamethasone	N/A	2
			carboplatin	N/A	2
CDK1	flavopiridol	0.990	eltrombopag	agonist	1
	aminopurvalanol a	0.997	romiplostim	agonist	1
	dinaciclib	0.971			
	purvalanol	0.970			
AKT1	rapamycin	0.996	arsenic trioxide	inducer	6
			everolimus	inhibitor	3
			vemurafenib	N/A	3
			irinotecan	N/A	2
			doxorubicin	N/A	2
	mk-2206 dihydrochloride	0.996	sirolimus	N/A	2
	MgATP	0.993	temsirolimus	N/A	2
	azd5363	0.992	cetuximab	N/A	2
			paclitaxel	N/A	1
EIF3F	phosphate	0.952	No interactions with FDA approved drugs found.		
	MgADP	0.900			
	MgATP	0.900			
	guanosine diphosphate	0.900			
UBC	zn(ii)	0.983	No interactions with FDA approved drugs found.		
	3h-proline	0.950			
	arginine	0.934			
	methionine	0.933			
PRKDC	MgATP	0.992	No interactions with FDA approved drugs found.		
	wortmannin	0.945			
	dna-pk inhibitor ii	0.928			
	torin2	0.901			

TRAF6	MgATP	0.915	No interactions with FDA approved drugs found.		
	MgADP	0.900			
	adenosine monophosphate	0.900			
	pyrophosphate	0.900			
PRKCA	MgATP	0.900	vitamin e	N/A	6
	MgADP	0.900	ingenol mebutate	activator, ligand	4
	calcium ions	0.900	tamoxifen	N/A	2

Table 15 Level 2 key gene-drug interaction analysis

Key Genes	STITCH ^{88,89}		DGIdb ⁹⁰		
	FDA approved Drug/chemical	Network interaction score (>0.9)	FDA approved Drug	Interaction Type	Score
APP	calcium ions	0.994	flutemetamol f18	binder	2
			propofol	N/A	2
			daunorubicin	N/A	2
			hydroxychloroquine	N/A	2
			florbetapir f 18	binder	2
			[18f] florbetaben	binder	1
NTRK1	antibiotic SF-2370	0.996	interferon gama-1b	N/A	3
			crizotinib	N/A	3
			cytarabine	N/A	2
			acetylcysteine	N/A	2
			phenylephrine	N/A	2
	lestaurtinib	0.996	regorafenib	inhibitor	2
			imatinib	N/A	2
			estradiol	N/A	2
			pyridoxine	N/A	2
GRB2	guanosine triphosphate	0.942	pegademase bovine	binder	2
	cadmium	0.929	dactinomycin	N/A	2
	AC1LCW0V	0.915			
	guanosine diphosphate	0.907			
EGFR	gefitinib	0.999	erlotinib	antagonist, inhibitor	167
			afatinib	inhibitor	141
	erlotinib	0.999	gefitinib	antagonist, inhibitor	125
			cetuximab	antagonist, inhibitor, antibody	110
	afatinib	0.999	panitumumab	agonist, inhibitor, antibody, suppressor	32
			lapatinib	antagonist, inhibitor	31
	lapatinib	0.999	osimertinib	inhibitor	31
			vandetanib	inhibitor	12
			sirolimus	N/A	8
			necitumumab	antagonist, inhibitor, antibody	7
TP53	etoposide	0.993	doxorubicin	N/A	10
			bevacizumab	N/A	8
	MgATP	0.991	gemcitabine	N/A	7
			carboplatin	N/A	7
	5-fluorouracil	0.991	paclitaxel	N/A	4
			docetaxel	N/A	4

	mitomycin C	0.989	sirolimus	N/A	4
			cyclophosphamide	N/A	4
			crizotinib	N/A	4
			oxaliplatin	N/A	4
ELAVL1	MgATP	0.914	No interactions with FDA approved drugs found.		
	MgADP	0.900			
NXF1	No interactions with FDA approved drugs/chemicals found.		No interactions with FDA approved drugs found.		
XPO1	guanosine triphosphate	0.987	No interactions with FDA approved drugs found.		
	MgADP	0.920			
	phosphate	0.917			
	MgATP	0.914			
MEOX2	No interactions with FDA approved drugs/chemicals found.		No interactions with FDA approved drugs found.		
BAG3	No interactions with FDA approved drugs/chemicals found.		No interactions with FDA approved drugs found.		

Application of Algorithm S1 (PDS_CS) on in the host targets of *in vitro* generated Human-nCoV PPIN of Gordon *et al.*⁹¹.

Gordon *et al.*⁹¹ cloned, tagged and expressed 26 of the 29 SARS-CoV-2 proteins in human cells and identified the human proteins that physically associated with each of the SARS-CoV-2 proteins using affinity-purification mass spectrometry, identifying 332 high-confidence protein-protein interactions between SARS-CoV-2 and human proteins. These 332 host targets are collected and Algorithm S1 (PDS_CS) is implemented on the same. It is observed from the implementation that Fostamatinib/R406 has a significant overlap of 10 target proteins (i.e., DCS score of 10) in Human-nCoV PPIN which is also the highest frequency of occurrence in the entire PPIN when compared to the remaining human protein associated drugs. The result is highlighted in the below table.

Detailed analysis of DCS score (Top 6 DCS have been shown)

Drug	Drug ID	DCS (Level 1)
Fostamatinib	DB12010	10
NADH	DB00157	5
Flavin adenine dinucleotide	DB03147	5
Romidepsin	DB06176	2
Glutamic acid	DB00142	2
Atorvastatin	DB01076	1

Conclusion

In this computational study, we have analyzed the Human-nCoV PPIN and attempted to identify the candidate drugs for the level-1 and level-2 spreader proteins. Our study identifies Fostamatinib, a FDA approved drug, as the most promising drug with best chances to target the COVID-19 spreader proteins. This drug may be considered as a potential candidate for COVID-19 treatment and related clinical trials.

Our work relies on the hypothesis that SARS-CoV 2/nCoV is believed to have ~89% genetic resemblance with SARS-CoV. Based on this, we have developed Human-nCoV PPIN by the identification of spreader nodes using SIS model and fuzzy thresholding. A consensus strategy by a two-way analysis has been utilized to analyze drugs based on the overlap of spreader proteins and drug protein targets. The consensus scores for Fostamatinib are highest in both the analysis among the candidate drugs for COVID-19 spreader proteins. Besides, it also generates the best results in molecular docking with the available COVID19 protein structures. These findings affirm that Fostamatinib might be one of the candidate drugs on COVID19, and worth a thorough clinical trial. Fostamatinib also targets CAYP34A^{46,47}, a common target for almost all the FDA approved drugs³⁴ for COVID-19. Moreover, recent studies also suggest that Fostamatinib is used for

thrombocytopenia⁴⁶ which is also associated with severe coronavirus disease 2019 (COVID-19) infections⁴⁸. In a nutshell, our computational research evidences discover the fact that Fostamatinib may be considered as one of the strong contenders for COVID-19 treatment and necessary trials may be initiated for clinical validations.

References

1. Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations. <https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations>.
2. Li, G. & De Clercq, E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nature reviews. Drug discovery* vol. 19 149–150 (2020).
3. WHO Coronavirus Disease (COVID-19) Dashboard. <https://covid19.who.int/>.
4. Cortegiani, A., Ingoglia, G., Ippolito, M., Giarratano, A. & Einav, S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *J. Crit. Care* (2020) doi:10.1016/j.jcrc.2020.03.005.
5. Zhang, Q., Wang, Y., Qi, C., Shen, L. & Li, J. Clinical trial analysis of 2019-nCoV therapy registered in China. *J. Med. Virol.* **92**, 540–545 (2020).
6. Rabby, M. I. I. Current drugs with potential for treatment of covid-19: A literature review. *J. Pharm. Pharm. Sci.* **23**, 58–64 (2020).
7. Zhang, W. *et al.* The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The experience of clinical immunologists from China. *Clinical Immunology* vol. 214 (2020).
8. Gautret, P. *et al.* Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int. J. Antimicrob. Agents* 105949 (2020) doi:10.1016/j.ijantimicag.2020.105949.
9. Runfeng, L. *et al.* Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2). *Pharmacol. Res.* **156**, 104761 (2020).
10. Liu, J. *et al.* Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discovery* vol. 6 1–4 (2020).
11. Sahraei, Z., Shabani, M., Shokouhi, S. & Saffaei, A. Aminoquinolines against coronavirus disease 2019 (COVID-19): chloroquine or hydroxychloroquine. *Int. J. Antimicrob. Agents* **55**, (2020).
12. Cai, Q. *et al.* Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. *Engineering* (2020) doi:10.1016/j.eng.2020.03.007.
13. Wu, D. & Yang, X. O. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Fedratinib. *J. Microbiol. Immunol. Infect.* (2020) doi:10.1016/j.jmii.2020.03.005.
14. Yao, X. *et al.* In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Main point: Hydroxychloroquine was found to be more potent than chloroquine at inhibiting SARS-CoV-2 in vit. *Clin. Infect. Dis.* **2**, 1–25 (2020).
15. Tang, B. *et al.* Coronavirus Disease 2019 (COVID-19) Pneumonia in a Hemodialysis Patient. *Kidney Med.* (2020) doi:10.1016/j.xkme.2020.03.001.
16. Fan, H. H. *et al.* Repurposing of clinically approved drugs for treatment of coronavirus disease 2019 in a 2019-novel coronavirus (2019-nCoV) related coronavirus model. *Chin. Med. J. (Engl)*. **133**, (2020).
17. Ren, J. ling, Zhang, A. H. & Wang, X. J. Traditional Chinese medicine for COVID-19 treatment. *Pharmacological Research* vol. 155 (2020).
18. Stebbing, J. *et al.* COVID-19: combining antiviral and anti-inflammatory treatments. *The Lancet Infectious Diseases* vol. 20 400–402 (2020).
19. Gordon, C. J., Tchesnokov, E. P., Feng, J. Y., Porter, D. P. & Götte, M. The antiviral compound remdesivir potently inhibits RNAdependent RNA polymerase from Middle East respiratory syndrome coronavirus. *Journal of Biological Chemistry* vol. 295 4773–4779 (2020).
20. Nguyen, T. M., Zhang, Y. & Pandolfi, P. P. Virus against virus: a potential treatment for 2019-nCov (SARS-CoV-

- 2) and other RNA viruses. *Cell Research* vol. 30 189–190 (2020).
21. ML, S., JM, Y., YP, S. & GH, S. Inhibitors of RAS Might Be a Good Choice for the Therapy of COVID-19 Pneumonia. *Zhonghua Jie He He Hu Xi Za Zhi* **43**, (2020).
 22. Lim, J. *et al.* Case of the index patient who caused tertiary transmission of coronavirus disease 2019 in Korea: The application of lopinavir/ritonavir for the treatment of COVID-19 pneumonia monitored by quantitative RT-PCR. *J. Korean Med. Sci.* **35**, (2020).
 23. Kruse, R. L. Therapeutic strategies in an outbreak scenario to treat the novel coronavirus originating in Wuhan, China [version 2; peer review: 2 approved]. *F1000Research* vol. 9 (2020).
 24. Wang, M. *et al.* Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research* vol. 30 269–271 (2020).
 25. Wang, Z., Chen, X., Lu, Y., Chen, F. & Zhang, W. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. *Biosci. Trends* **14**, (2020).
 26. Holshue, M. L. *et al.* First Case of 2019 Novel Coronavirus in the United States. *N. Engl. J. Med.* **382**, 929–936 (2020).
 27. H.L. Zhang & Y.X. Zhu. One highly suspected case of novel coronavirus pneumonia treated by Integrated Traditional Chinese and Western medicine and nucleic acid analysis. *Tianjin J. Tradit. Chinese Med.*
 28. Blanco, J. L. *et al.* COVID-19 in patients with HIV: clinical case series. *The Lancet HIV* vol. 7 e314–e316 (2020).
 29. Lancet, I. T. & Wang, Y. Remdesivir for COVID-19: challenges of underpowered studies. *Lancet* **6736**, 31022–31023 (2020).
 30. COVID-19 Studies from the World Health Organization Database - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/who_table.
 31. Saha, S., Sengupta, K., Chatterjee, P., Basu, S. & Nasipuri, M. Analysis of protein targets in pathogen–host interaction in infectious diseases: a case study on Plasmodium falciparum and Homo sapiens interaction network. *Brief. Funct. Genomics* **17**, 441–450 (2017).
 32. Halder, A. K., Dutta, P., Kundu, M., Basu, S. & Nasipuri, M. Review of computational methods for virus–host protein interaction prediction: a case study on novel Ebola–human interactions. *Brief. Funct. Genomics* **17**, 381–391 (2018).
 33. Bailey, N. T. J. The mathematical theory of infectious diseases and its applications. 2nd edition. *Math. theory Infect. Dis. its Appl. 2nd Ed.* (1975).
 34. Lucy Chin, Jordan Cox, Safiya Esmail, Mark Franklin, D. Le. COVID-19: Finding the Right Fit Identifying Potential Treatments Using a Data-Driven Approach. *Drugbank White Pap.* (2020).
 35. Fostamatinib - DrugBank. <https://www.drugbank.ca/drugs/DB12010>.
 36. Drug Approval Package: TAVALISSE (fostamatinib disodium hexahydrate). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/209299Orig1s000TOC.cfm.
 37. Saha, S., Chatterjee, P., Basu, S. & Nasipuri, M. Detection of spreader nodes and ranking of interacting edges in Human-SARS-CoV protein interaction network. *bioRxiv* 2020.04.12.038216 (2020) doi:10.1101/2020.04.12.038216.
 38. Saha, S. *et al.* Computational modeling of Human-nCoV protein-protein interaction network. (2020).
 39. Wishart, D. S. *et al.* DrugBank: a knowledgebase for drugs, drug actions and drug targets. *Nucleic Acids Res.* **36**, D901–D906 (2008).
 40. DrugBank. <https://www.drugbank.ca/>.
 41. Kumar, S. COVID-19: A drug repurposing and biomarker identification by using comprehensive gene–disease associations through protein–protein interaction network analysis. *Preprints* (2020) doi:10.20944/preprints202003.0440.v1.
 42. Piñero, J. *et al.* DisGeNET: a discovery platform for the dynamical exploration of human diseases and their genes.

Database (Oxford). **2015**, bav028–bav028 (2015).

43. MULTIPLE LIST COMPARATOR - A free online tool to find list overlaps and draw Venn diagrams. <http://molbiotools.com/listcompare.html>.
44. Mattingly, C. J., Rosenstein, M. C., Colby, G. T., Forrest, J. N. & Boyer, J. L. The Comparative Toxicogenomics Database (CTD): A resource for comparative toxicological studies. in *Journal of Experimental Zoology Part A: Comparative Experimental Biology* vol. 305 689–692 (2006).
45. FDA approves fostamatinib tablets for ITP | FDA. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-fostamatinib-tablets-ityp>.
46. McKeage, K. & Lyseng-Williamson, K. A. Fostamatinib in chronic immune thrombocytopenia: a profile of its use in the USA. *Drugs Ther. Perspect.* **34**, 451–456 (2018).
47. Fujita, K. I. Food-drug interactions via human cytochrome P450 3A (CYP3A). *Drug Metabolism and Drug Interactions* vol. 20 195–217 (2004).
48. Lippi, G., Plebani, M. & Henry, B. M. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. *Clin. Chim. Acta* **506**, 145–148 (2020).
49. Jin, Z. *et al.* Structure of Mpro from COVID-19 virus and discovery of its inhibitors. *Nature* 1–9 (2020) doi:10.1038/s41586-020-2223-y.
50. Agrawal, M., Zitnik, M. & Leskovec, J. Large-Scale Analysis of Disease Pathways in the Human Interactome. *bioRxiv* 189787 (2017) doi:10.1101/189787.
51. BioSNAP: Network datasets: Human protein-protein interaction network. <https://snap.stanford.edu/biodata/datasets/10000/10000-PP-Pathways.html>.
52. Pfefferle, S. *et al.* The SARS-Coronavirus-host interactome: Identification of cyclophilins as target for pan-Coronavirus inhibitors. *PLoS Pathog.* **7**, (2011).
53. Bateman, A. *et al.* UniProt: The universal protein knowledgebase. *Nucleic Acids Res.* **45**, D158–D169 (2017).
54. Chan, J. F. W. *et al.* Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg. Microbes Infect.* **9**, 221–236 (2020).
55. China releases genetic data on new coronavirus, now deadly | CIDRAP. <https://www.cidrap.umn.edu/news-perspective/2020/01/china-releases-genetic-data-new-coronavirus-now-deadly>.
56. Samadi, N. & Bouyer, A. Identifying influential spreaders based on edge ratio and neighborhood diversity measures in complex networks. *Computing* **101**, 1147–1175 (2019).
57. Wang, S. & Wu, F. Detecting overlapping protein complexes in PPI networks based on robustness. *Proteome Sci.* **11**, 1–8 (2013).
58. Dutta, P., Basu, S. & Kundu, M. Assessment of Semantic Similarity between Proteins Using Information Content and Topological Properties of the Gene Ontology Graph. *IEEE/ACM Trans. Comput. Biol. Bioinforma.* **15**, 839–849 (2018).
59. Consortium, G. O. & others. The Gene Ontology (GO) database and informatics resource. *Nucleic Acids Res* **32**, D258–D261 (2004).
60. Emergency Use Authorization | FDA. <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>.
61. Harrison, C. Coronavirus puts drug repurposing on the fast track. *Nat. Biotechnol.* (2020) doi:10.1038/d41587-020-00003-1.
62. Cao, B. *et al.* A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. *N. Engl. J. Med.* (2020) doi:10.1056/nejmoa2001282.
63. de Wit, E. *et al.* Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc. Natl. Acad. Sci. U. S. A.* **117**, 6771–6776 (2020).
64. Emergency Access to Remdesivir Outside of Clinical Trials. <https://www.gilead.com/purpose/advancing-global-health/covid-19/emergency-access-to-remdesivir-outside-of-clinical-trials>.

65. Remdesivir Clinical Trials. <https://www.gilead.com/purpose/advancing-global-health/covid-19/remdesivir-clinical-trials>.
66. China approves antiviral favilavir to treat coronavirus - UPI.com. https://www.upi.com/Health_News/2020/02/17/China-approves-antiviral-favilavir-to-treat-coronavirus/5291581953892/.
67. Taiwan synthesizes anti-viral drug favilavir for COVID-19 patients - Focus Taiwan. <https://focustaiwan.tw/sci-tech/202003020012>.
68. Lu, R. *et al.* Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* **395**, 565–574 (2020).
69. Ciaglia, E., Vecchione, C. & Puca, A. A. COVID-19 Infection and Circulating ACE2 Levels: Protective Role in Women and Children. *Front. Pediatr.* **8**, 206 (2020).
70. Xiao, H., Xu, L. H., Yamada, Y. & Liu, D. X. Coronavirus spike protein inhibits host cell translation by interaction with eIF3f. *PLoS One* **3**, (2008).
71. Ma-Lauer, Y. *et al.* P53 down-regulates SARS coronavirus replication and is targeted by the SARS-unique domain and PLpro via E3 ubiquitin ligase RCHY1. *Proc. Natl. Acad. Sci. U. S. A.* **113**, E5192–E5201 (2016).
72. Wendt, L. *et al.* The Ebola Virus Nucleoprotein Recruits the Nuclear RNA Export Factor NXF1 into Inclusion Bodies to Facilitate Viral Protein Expression. *Cells* **9**, 187 (2020).
73. Luo, C. *et al.* Nucleocapsid protein of SARS coronavirus tightly binds to human cyclophilin A. *Biochem. Biophys. Res. Commun.* **321**, 557–565 (2004).
74. Nigro, P., Pompilio, G. & Capogrossi, M. C. Cyclophilin A: A key player for human disease. *Cell Death and Disease* vol. 4 e888 (2013).
75. Chai, Q. *et al.* HIV-1 counteracts an innate restriction by amyloid precursor protein resulting in neurodegeneration. *Nat. Commun.* **8**, (2017).
76. Chen, Z. *et al.* GRB2 Interaction with the Ecotropic Murine Leukemia Virus Receptor, mCAT-1, Controls Virus Entry and Is Stimulated by Virus Binding. *J. Virol.* **86**, 1421–1432 (2012).
77. Venkataraman, T. & Frieman, M. B. The role of epidermal growth factor receptor (EGFR) signaling in SARS coronavirus-induced pulmonary fibrosis. *Antiviral Research* vol. 143 142–150 (2017).
78. Meng, X.-Y., Zhang, H.-X., Mezei, M. & Cui, M. Molecular Docking: A powerful approach for structure-based drug discovery. *Curr. Comput. Aided. Drug Des.* **7**, 146 (2011).
79. RCSB PDB - 6LU7: The crystal structure of COVID-19 main protease in complex with an inhibitor N3. <https://www.rcsb.org/structure/6lu7>.
80. Stella, V. J., Charman, W. N. A. & Naringrekar, V. H. Prodrugs. *Drugs* **29**, 455–473 (1985).
81. Baluom, M., Grossbard, E. B., Mant, T. & Lau, D. T. W. Pharmacokinetics of fostamatinib, a spleen tyrosine kinase (SYK) inhibitor, in healthy human subjects following single and multiple oral dosing in three phase I studies. *Br. J. Clin. Pharmacol.* **76**, 78–88 (2013).
82. RCSB PDB - 3FQS: Crystal structure of spleen tyrosine kinase complexed with R406. <https://www.rcsb.org/structure/3fqs>.
83. Villaseñor, A. G. *et al.* Structural Insights for Design of Potent Spleen Tyrosine Kinase Inhibitors from Crystallographic Analysis of Three Inhibitor Complexes. *Chem. Biol. Drug Des.* **73**, 466–470 (2009).
84. RCSB PDB - 6K32: RdRp complex. <https://www.rcsb.org/structure/6K32>.
85. Li, X. *et al.* Structure of RdRps Within a Transcribing dsRNA Virus Provides Insights Into the Mechanisms of RNA Synthesis. *J. Mol. Biol.* **432**, 358–366 (2020).
86. Tavakolian, S., Goudarzi, H. & Faghihloo, E. Cyclin-dependent kinases and CDK inhibitors in virus-associated cancers. *Infectious Agents and Cancer* vol. 15 1–12 (2020).
87. ZFIN Gene: ntrk1. <https://zfin.org/ZDB-GENE-980526-118>.

88. Kuhn, M., von Mering, C., Campillos, M., Jensen, L. J. & Bork, P. STITCH: interaction networks of chemicals and proteins. *Nucleic Acids Res.* **36**, D684–D688 (2008).
89. Szklarczyk, D. *et al.* STITCH 5: augmenting protein-chemical interaction networks with tissue and affinity data. *Nucleic Acids Res.* **44**, D380–D384 (2016).
90. Griffith, M. *et al.* DGIdb: Mining the druggable genome. *Nat. Methods* **10**, 1209–1210 (2013).
91. Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, White KM, *et al.* A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* 2020;583:459–68. <https://doi.org/10.1038/s41586-020-2286-9>.

Acknowledgements

This work is partially supported by the CMATER research laboratory of the Computer Science and Engineering Department, Jadavpur University, India, PURSE-II and UPE-II grants. Subhadip Basu acknowledges Department of Biotechnology grant (BT/PR16356/BID/7/596/2016), Government of India. For research fellowship support, Anup Kumar Halder acknowledges the Visvesvaraya PhD Scheme for Electronics & IT, an initiative of Ministry of Electronics & Information Technology (MeitY), Government of India. We acknowledge Prof. Jacek Sroka (Institute of Informatics, University of Warsaw) for his contribution toward the developments of the fuzzy ppi methods.

Author contributions statement

S.S., A.K.H. and S.B. conceived the idea of the research and wrote the manuscript. S.S. and A.K.H. conducted the experiment(s). P.C., S.S.B., M.N., D.B. and S.B. analyzed the results. M.N., P.C. and S.B. reviewed the manuscript.

Additional information

Competing interests: The authors declare no competing interests.

All queries should be sent to the corresponding author's email: subhadip.basu@jadavpuruniversity.in