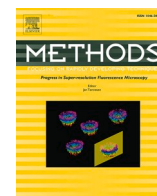




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Drug repurposing for COVID-19 using computational screening: Is Fostamatinib/R406 a potential candidate?

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ABSTRACT

With the gradual increase in the COVID-19 mortality rate, there is an urgent need for an effective drug/vaccine. Several drugs like Remdesivir, Azithromycin, Favirapir, Ritonavir, Darunavir, etc., are put under evaluation in more than 300 clinical trials to treat COVID-19. On the other hand, several vaccines like Pfizer-BioNTech, Moderna, Johnson & Johnson's Janssen, Sputnik V, Covishield, Covaxin, etc., also evolved from the research study. While few of them already gets approved, others show encouraging results and are still under assessment. In parallel, there are also significant developments in new drug development. But, since the approval of new molecules takes substantial time, drug repurposing studies have also gained considerable momentum. The primary agent of the 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, Human-SARS-CoV protein interactions are used to develop an *in-silico* Human-nCoV network by identifying potential COVID-19 human spreader proteins by applying the SIS model and fuzzy thresholding by a possible COVID-19 FDA drugs target-based validation. At first, the complete list of FDA drugs is identified for the level-1 and level-2 spreader proteins in this network, followed by applying a drug consensus scoring strategy. The same consensus strategy is involved in the second analysis but on a curated overlapping set of key genes/proteins identified from COVID-19 symptoms. Validation using subsequent docking study has also been performed on COVID-19 potential drugs with the available major COVID-19 crystal structures whose PDB IDs are: 6LU7, 6M2Q, 6W9C, 6M0J, 6M71 and 6VXX. Our computational study and docking results suggest that Fostamatinib (R406 as its active moiety) may also be considered as one of the potential candidates for further clinical trials in pursuit to counter the spread of COVID-19.

1. Introduction

The world has witnessed several severe epidemics like Spanish flu, ebola, cholera etc. Now we are in front of the most life-threatening viral outbreak with COVID-19. The feature that makes this new coronavirus, nCoV, unique is its ability to quickly transmit through an infected COVID patient [1]. The virus causing COVID-19 is an assimilation of accessory, non-structural and structural proteins [2]. According to

World Health Organization (WHO) coronavirus disease dashboard [3], 162,704,139 confirmed cases of COVID-19, including 3,374,052 deaths, have been reported as of 1:39 pm CEST, 17 May 2021. Based on the prior knowledge of major outbreaks of Ebola, cholera etc., treatments with different antiviral drugs are considered and implemented to terminate COVID-19 based on previous knowledge of significant attacks. A literature survey [4] is recently carried out through a refined computational search in various online repositories like Google Scholar, Science Direct,

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PubMed, etc., to enlist various COVID-19 drug-related research articles since the onset of this pandemic. Almost 22 most relevant COVID-19 related drug articles [4] have been filtered out from the search results. All these significant researches and some others have been extensively studied, the details of which have been listed in the [supplementary Table S1](#).

It is noted from [Table S1](#) that the most recommended drugs are azithromycin, lopinavir, ritonavir, remdesivir, and favipiravir. It also appears 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 the 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 whether the COVID infected patient recovers due to applying the suggested drug or recover due to extensive clinical care and isolation. However, some of the *in vitro* studies have shown favourable results for these drugs. Still, these are all preliminary data, which need much more evidence before putting it in clinical trial.

COVID-19 vaccines are also in the same race as COVID-19 drugs. According to a current report [5] by the Centers for Disease Control and Prevention (CDC), Pfizer-BioNTech, Moderna, and Johnson & Johnson's Janssen are the recommended and authorized vaccines in the United States COVID-19. In addition, another vaccine Sputnik V has been developed by Gamaleya National Center in Russia. Though it is found effective in initial trials, it has been recommended only for emergency use by the Technical Advisory Group (TAG) of WHO [6]. In contrast, Covishield [7] and Covaxin [8] are the recommended vaccines in India. All these vaccines might have specific side effects which need further analysis and research. But the two significant areas of concern are: 1) it is still unknown whether these vaccines are effective against all COVID-19 strains and 2) "getting vaccinated" does not guarantee that COVID-19 will not happen again. Still, it says it could save somebody's life by refraining from getting seriously ill if they get infected with COVID-19. So, vaccines do not provide any herd immunity.

Due to the daily increase in deaths [9], there is an urgent need to identify a potential vaccine/drug that will eventually help eradicate COVID-19. So, with no other alternatives left, clinical trials have been started by WHO [10] on all the suggested drugs, including the ones mentioned in [Table S1](#), which are somehow proved to be substantially beneficial in case studies of COVID-19. Drug design needs a proper understanding of disease transmission mechanisms that can be effectively done by analysing Host-pathogen protein–protein interaction networks (PPIN) [10]. Pathogen facilitates disease progression as it has the potential to transform itself by mutation. Infection of pathogen gets broadcasted through the connecting edge of interaction between host and pathogen. Thus, it is essential to explore target proteins and their interactions in Host-pathogen protein–protein interaction [11] networks for potential drug discovery [12]. However, the only recognized *in vitro* Human-nCoV PPIN available to date is in the work of Gordon *et al.* [13]. But UniProt reviewed nCoV proteins cannot be mapped through this *in vitro* generated PPIN. So, all this lead to the development of an *in silico* Human-nCoV PPIN through the SIS model [14] and fuzzy thresholding. Further study of protein targets of potential Food and Drug Administration (FDA) drugs [15] of COVID-19 in the formed Human-nCoV PPIN network also shows that FDA approved drug, Fostamatinib (R406 as its active moiety) [16], can be a potential drug for COVID-19 treatment. Rigel Pharmaceuticals, Inc. [17] got approval for TAVALISSE (Fostamatinib disodium hexahydrate) for the treatment of Chronic Immune Thrombocytopenia [18] from the FDA on 17/04/2018.

The major contribution of the proposed work is described as follows: 1) It uses an *in silico* model which has been developed to identify potential spreader proteins in a Human-nCoV interaction network in the work of Saha *et al.* [19,20], which was validated using proteins which are the targets of potential FDA drugs [15] for COVID-19 treatment. 2) A two-way analysis: a) Human-nCoV interaction network analysis b) COVID-19 symptom [21] based analysis (including "loss of smell"), have been implemented to detect the potential candidates in the list of FDA

drugs for COVID-19. 3) In both the analyses, Fostamatinib/R406 [16], an FDA approved drug and commonly used for the treatment of chronic immune thrombocytopenia (ITP) [22], ranks at the top having a maximum overlap of target proteins in the Human-nCoV interaction network. 4) Fostamatinib/R406 is used for thrombocytopenia [23] which is also associated with severe coronavirus disease 2019 (COVID-19) infections [24]. 5) Molecular docking has also been performed on Fostamatinib/R406 and other potential FDA drugs [15] with the available major COVID-19 crystal structures having PDB IDs: 6LU7 [25], 6M2Q [26], 6W9C [27], 6M0J [28], 6M71 [29] and 6VXX [30]. While Fostamatinib registers the highest score for 6LU7 and 6M2Q, it obtains a second position than the other COVID-19 structures. 6) The active moiety of Fostamatinib, i.e., R406, generates the highest docking scores compared to all other active metabolites. The detailed analysis of this entire methodology has been discussed in the subsequent sections and [supplementary document](#).

2. Methods

The proposed methodology involves 4 datasets: 1) Human PPIN [31,32] 2) SARS-CoV PPIN [33] 3) SARS-CoV-Human PPIN [33] and 4) SARS-CoV2 proteins [34]. The overall dataset statistics are highlighted in [Table 1](#). The entire proposed methodology of drug repurposing can be categorized into four major sections.

2.1. Detection of spreader nodes in Human-nCoV PPIN

The only recognized *in vitro* Human-nCoV PPIN available to date is in the work of Gordon *et al.* [13]. But UniProt reviewed nCoV proteins cannot be mapped through this *in vitro* generated PPIN. 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 [35,36] with SARS-CoV2. Not every protein in a PPIN is a spreader protein/node. Spreader proteins are considered to be those specific proteins that have a unique fast capability of transmitting infection in their neighbourhood in a short time [19]. They are identified through spreadability index computed by the combination of three terminologies: 1) Edge ratio [37], 2) Neighbourhood density [37] and 3) node weight [38]. Proteins having a high spreadability index are spreader proteins (for more details, please see supplementary). Identification of spreader proteins is conducted initially in the SARS-CoV PPIN dataset. Corresponding connected human proteins, i.e., level 1 and level 2 of selected SARS-CoV spreader proteins, are chosen from SARS-CoV-Human PPIN and Human PPIN datasets. Hence, the spreadability index detects spreader proteins in level 1 and 2 human proteins of SARS-CoV. The selected spreader nodes are also validated by Susceptible-Infected-Susceptible (SIS) model [14] (see [Fig. 1](#)). This results in forming a PPIN consisting of 7 SARS-CoV, 24 level 1 and 111 level 2 human spreader proteins, respectively, under a low threshold [19]. The potential Human-nCoV interactions have been identified using developed *in silico* fuzzy PPI model [39]. In this model, SARS-COV spreader (level-1 and level-2) proteins in humans are considered the candidate set of interactors for nCoV [20]. The nCoV-Human pair-wise relationships are

Table 1
Description and details of the datasets.

Database Name	Description	Nodes	Interactions/ Edges
Human PPIN	Human-human protein interactions	21,557	342,353
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	—

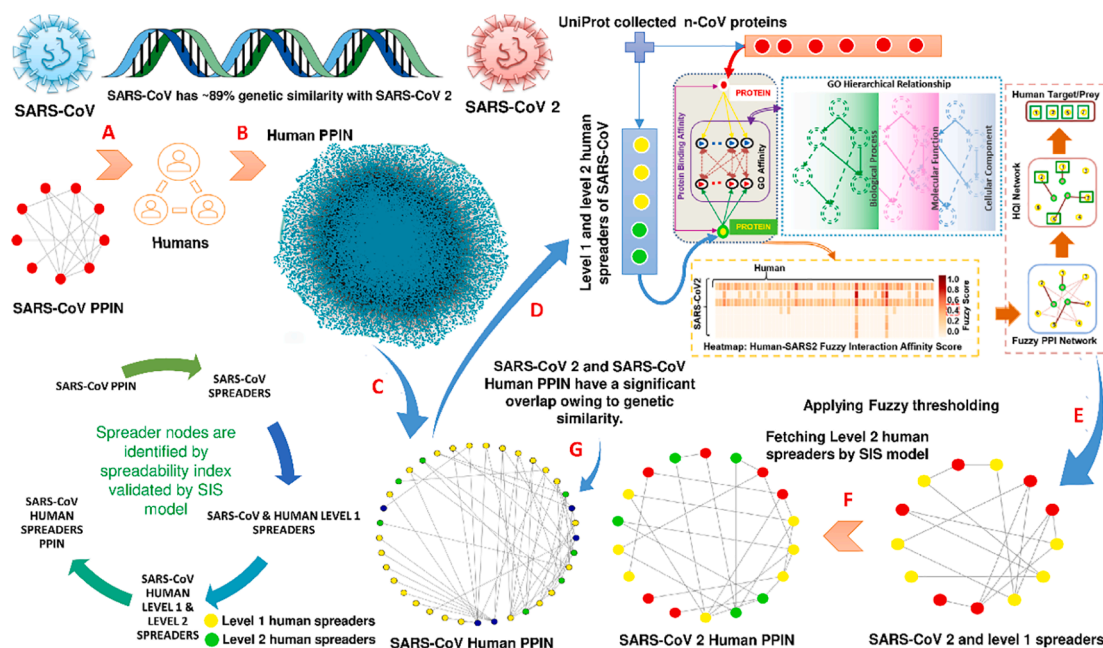


Fig. 1. The schematic diagram for the construction of COVID-19-Human PPIN. A. Formation of SARS-CoV PPIN (Red nodes) B. Formation of Human PPIN C. Spreader nodes identification in SARS-CoV-Human PPIN which is formed by the application of *spreadability index* and SIS model (Blue nodes represent SARS-CoV spreaders, while yellow and green denote level-1 and level-2 human spreaders) D. UniProt collected n-CoV proteins along with level-1 and level-2 human spreader nodes in SARS-CoV-Human PPIN are provided as an input to fuzzy thresholding E. SARS-CoV2, and level-1 Human spreaders are identified based on Fuzzy score (Red nodes represent SARS-CoV2 spreaders, while yellow denote level-1 human spreaders) F. Level-2 Human spreaders are identified by the application of the SIS model (Green nodes represent level-2 human spreaders) G. SARS-CoV-Human PPIN and SARS-CoV2-Human PPIN have a significant overlap owing to its genetic similarity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

quantified using the semantic similarity of their annotated GO pairs. A hybrid approach has been applied to assess the semantic similarity between GO target pairs using the topological properties of three GO subgraphs (BP: Biological Process, MF: Molecular Function and CC: Cellular Component) [40]. 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 Fig. 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 prey [20].

2.2. Identification of potential candidate FDA drugs with respect to COVID19 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 DrugBank [41]. DrugBank is an online repository [42] that contains comprehensive data about drugs, drug-protein targets and information about drug metabolism. Due to the high-quality annotation in DrugBank, it becomes the most used database in almost all *in silico* methodologies involved in drug design, docking of drugs, and drug interaction prediction. It contains about 60% and 10% of FDA approved and experimental drugs, respectively [41]. On proper analysis, it has been observed that various spreader nodes in COVID19-human PPIN are the protein targets of potential COVID19 FDA listed drugs [15]: hydroxychloroquine [43,44], azithromycin [43], lopinavir [45], ritonavir [46], remdesivir [47-49], and favipiravir [50,51]. The details of significant overlap between spreader nodes and drug-protein targets are highlighted in Table 2 [20]. It is observed from Table 2 that hydroxychloroquine has the highest hit/overlap, i.e. four, while each of azithromycin, lopinavir, ritonavir and darunavir has two hits [20]. Remdesivir and favipiravir have one impact individually [20].

Table 2

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

Remdesivir is the only drug that acts directly on COVID19 protein R1AB_SARS2. Significant overlapping drug targets and spreader nodes in Table 2 motivate us to analyse further and 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, defined as the frequency of occurrences of a drug at a particular level of PPIN. Execution of the PDS_CS algorithm is also highlighted in Fig. 2 by considering a sample (randomly generated COVID19-Human PPIN). In this PPIN, corresponding linked drugs are mapped with each human protein (marked as green) in level-1 and level-2, as shown in Table A in Fig. 2. Hence the DCS, i.e., frequency of each drug, is computed and highlighted in Table B in Fig. 2. Since Fostamatinib has the highest DCS in both levels, it is considered the potential drug for the target nCoV protein in the randomly generated COVID19-Human PPIN (marked as red). Algorithm 1 is not only implemented in the *in silico* generated Human-nCoV PPIN [20] but also in the host targets of *in vitro* generated Human-nCoV PPIN of Gordon et al. [13] (for details, please see Section 3.6).

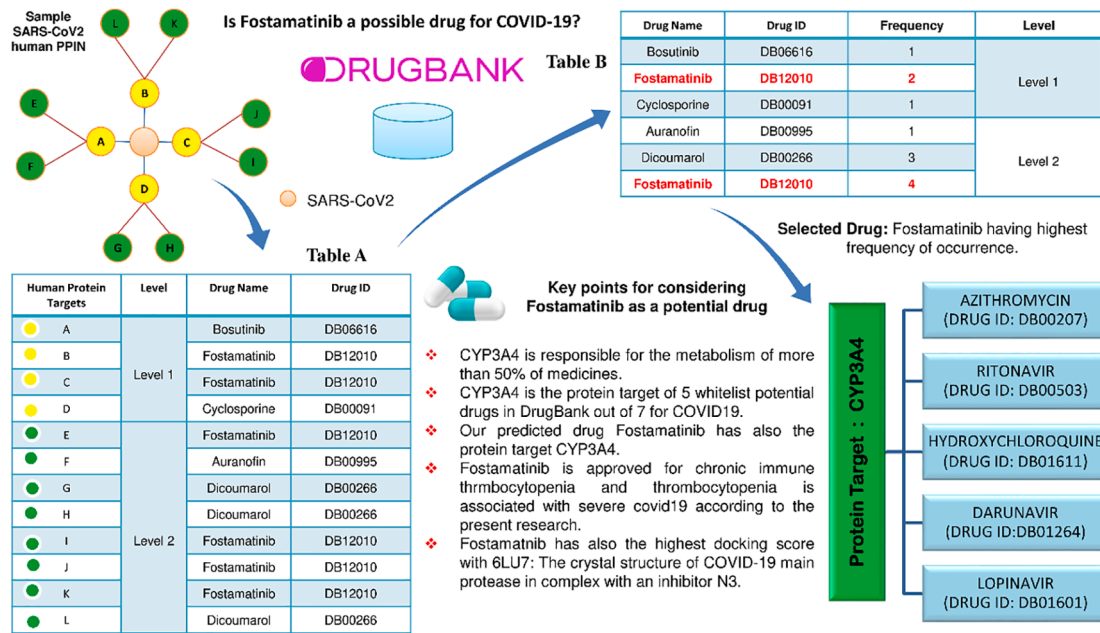


Fig. 2. A drug consensus score was adopted to choose Fostamatinib/R406 as a potential COVID19 drug. Other connecting biological links for selecting the same have also been highlighted.

2.3. Identification of potential candidate FDA drugs with respect to COVID19 spreader nodes using COVID19 symptoms, risk factors and clinical outcome-based analysis

COVID19 is associated with specific health symptoms like cough, fever, breathing difficulty, loss of smell etc. Usually, the symptom “loss of smell” plays a higher significant role in comparison to the other existing symptoms [52–54] (for more details, please see the supplementary

document). These symptoms are linked with specific human gene sets chosen as the bait’s possible targets (preys), 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 [46] from the disease-gene dataset available from DisGeNET. DisGeNET [55] is considered one of the significant resources covering all the relevant information about various diseases. These multiple gene sets are compared with each other [21] using molbiotools. The resultant gene set

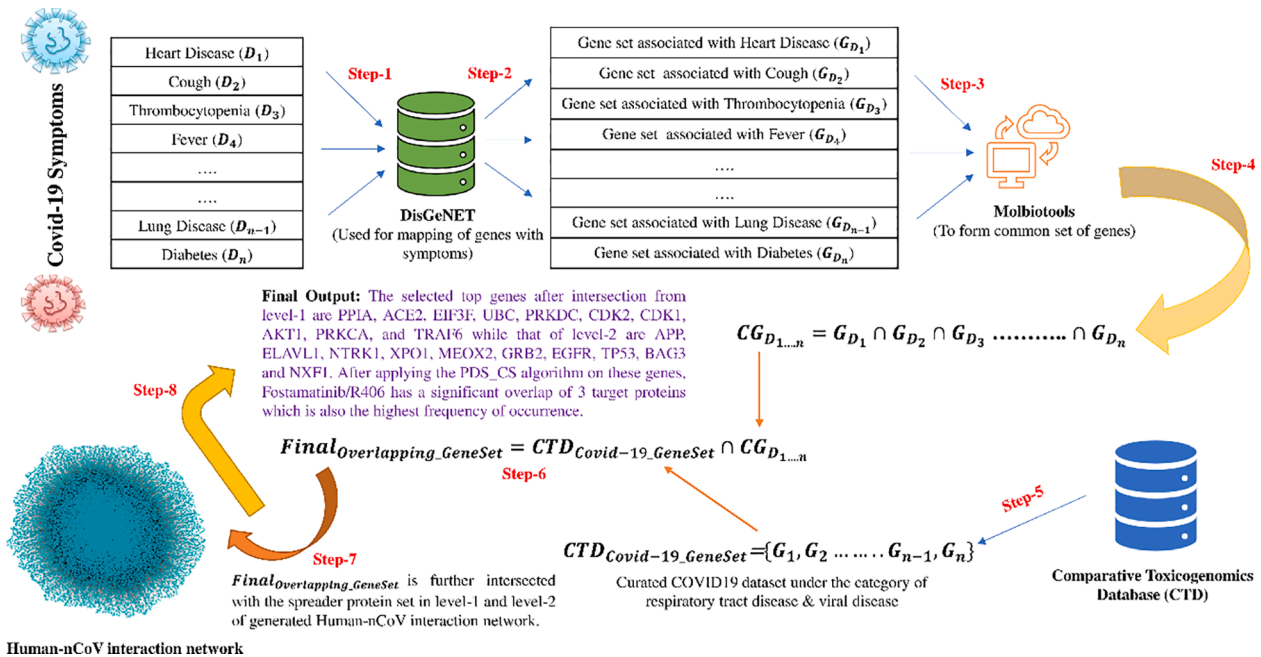


Fig. 3. Covid19 Symptoms based analysis. The analysis consists of the following steps. Step-1: Symptoms are searched in the DisGeNET database. Step-2: Symptom associated gene sets are fetched from the DisGeNET database. Step-3: All gene sets are provided as an input to Molbiotools online. Step-4: Common overlapping set of genes are obtained from Molbiotools. Step-5: Curated Covid19 dataset is extracted from the Comparative Toxicogenomics Database (CTD) under respiratory tract disease & viral disease. Step-6: These sets of genes intersect with the common overlapping set of genes obtained from Molbiotools to form a key set of Covid19 related genes. Step-7: This key set of Covid19 related genes, after mapping to their corresponding protein IDs, are compared with the spreader proteins in Human-nCoV PPI. Step-8: After comparison, top genes are selected in both level-1 and level-2 of Human-nCoV PPI, which are finally used for the PDS_CS algorithm to determine the most potential candidate FDA drug for COVID19. Here, Fostamatinib/R406 has the highest DCS score.

is again compared [21] with the curated COVID19 dataset available in Comparative Toxicogenomics Database [56] under respiratory tract disease & viral disease to obtain an overlapping gene set. CTD is yet another significant resource that 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 generated Human-nCoV interaction network [20]. The top 10 key genes are selected from the resultant intersection in each level based on the fuzzy score and spreadability index score in level-1 and level-2. These genes are considered the most significant ones that play an essential role in COVID19 transmission [57–61] and prevention [62–66] in the Human-nCoV interaction network. Potential FDA drugs having these key genes/spreader proteins as known targets are identified from DrugBank data [41,42]. Then PDS_CS algorithm is executed to determine the most potential candidate FDA drug for COVID19. The entire process of the symptom-based analysis is highlighted in Fig. 3.

2.4. Computational docking of potential drugs with respect to COVID19 protein structures

The earlier sections discuss how several SARS-CoV2 proteins like R1AB_SARS2, SPIKE_SARS2, R1A_SARS2 etc., react with the human level-1 and level-2 spreaders to form SARS-CoV2-Human PPIN. Hence, a drug repurposing study is done based on network and symptom-based analysis. It reveals Fostamatinib/R406 might be a potential drug for COVID-19. However, a docking study is required to light this further, stating how well Fostamatinib/R406 binds with the SARS-CoV2 proteins. One of the most powerful approaches for structure-based drug discovery is molecular docking. It is defined as analysing how more than one molecular structure (drug and protein or enzyme) gets attached [67]. In other words, docking can be interpreted as molecular modelling methodology, which is implemented to anticipate how small molecules, i.e., ligands, interrelate with protein, i.e., enzyme. But to do docking, proteins structures of both SARS-CoV2 proteins and Fostamatinib/R406 are required. So, protein–ligand docking is executed by using Molegro Virtual Docker (version: 6.0) on potential COVID19 FDA listed drugs, Fostamatinib and R406, with all the so far available protein structures on nCoV having PDB IDs: 6LU7 [25], 6M2Q [26], 6W9C [27], 6M0J [28], 6M71 [29], 6VXX [30]. Grid-based cavity prediction is used to identify the potential binding sites. Models involving flexible ligands are taken into consideration. Orientation of ligands usually differs, and ranking for each ligand is based on the energy scores. The entire algorithm is implemented at 1500 iterations with a simplex evolution size of 10 runs. Compounds that take the lowest binding energy in comparison to others are considered to be the best. The molecules of the potential COVID19 FDA listed drugs are downloaded from DrugBank [41] in Structure data file (SDF/PDB) format. The docking returns two types of scores: 1) Moldock scores and 2) Rerank scores (for more details, please see supplementary) [68]. 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, representing the lowest energy required to get tied up with amino acid (AA) components.

3. Results and discussion

Computational study and results of associated drugs with human proteins in Human-nCoV PPIN shows that there is a probability that Fostamatinib/R406 may act as one of the potential candidates for COVID-19 treatment.

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

Drugs and their corresponding IDs are mapped with all human spreader proteins in Human-nCoV PPIN by matching the related drug-

Table 3

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

Drug	Drug ID	DCS (Level 1)
Fostamatinib/R406	DB12010	7
Arsenic trioxide	DB01169	2
Acetylsalicylic acid	DB00945	2
Resveratrol	DB02709	2
Tamoxifen	DB00675	1

Table 4

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

Drug	Drug ID	DCS (Level 2)
Fostamatinib/R406	DB12010	148
Copper	DB09130	88
Zinc acetate	DB14487	57
Zinc	DB01593	57
Zinc chloride	DB14533	57

protein targets with spreader nodes. It is observed after applying the PDS_CS algorithm that Fostamatinib/R406 has a significant overlap of 155 target proteins 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 (i.e., highest Drug Consensus Score or DCS score as described earlier in the methodology section). It has a DCS score of 7 (i.e., count of level-1 protein targets of Fostamatinib as shown in Table 3) and 148 (i.e., count of level-2 protein targets of Fostamatinib as shown in Table 4) in level-1 and level-2 human spreader proteins. This establishes that the algorithm has succeeded in detecting the appropriate drug molecules with the highest protein targets in both levels. Protein targets corresponding to the DCS score of Fostamatinib in level-1 is highlighted in Fig. 4, while that of level-2 is shown in Fig. 5. In Fig. 4, green nodes represent level-1 protein targets of Fostamatinib, while blue and yellow nodes denote COVID-19 and other level-1 human proteins, respectively. In Fig. 5, green nodes represent level-2 protein targets of Fostamatinib, while blue and yellow nodes denote COVID-19 and other level-1 spreader human proteins, respectively. Other level-2 human spreaders in Fig. 5 are not shown to avoid visual complexity. The highest frequency of Fostamatinib/R406 is observed when the PDS_CS algorithm is implemented on Human-nCoV PPIN of Gordon et al. [13] (for more details, please see section 3.6).

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

Grouping genes based on various categories of COVID-19 symptoms, risk factors, and clinical outcomes [21] is done using DisGeNET [55]. The numerical statistics of the result is highlighted in supplementary Table S2. Mbiotools [69] are used to compare these gene sets to obtain 4931 unique genes. These genes are further compared with the curated COVID-19 dataset of CTD [56], containing 12,672 genes. The comparison generates an overlapping gene set containing 3525 genes. When used for validation against the spreader proteins in the Human-nCoV interaction network, these genes produce 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 the network. Hence, the top 10 key genes are selected from 1448 in each level based on the fuzzy and spreadability index scores in level-1 and level-2. The selected top genes from level-1 are PPIA, ACE2, EIF3F, UBC, PRKDC, CDK2, CDK1, AKT1, PRKCA, and TRAF6 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 (see the supplementary Table S3 and Table S4). It is also observed that after applying the PDS_CS algorithm on the obtained result in Table S3 and Table S4, Fostamatinib/R406 has a significant overlap of 3 target proteins which is also the highest frequency

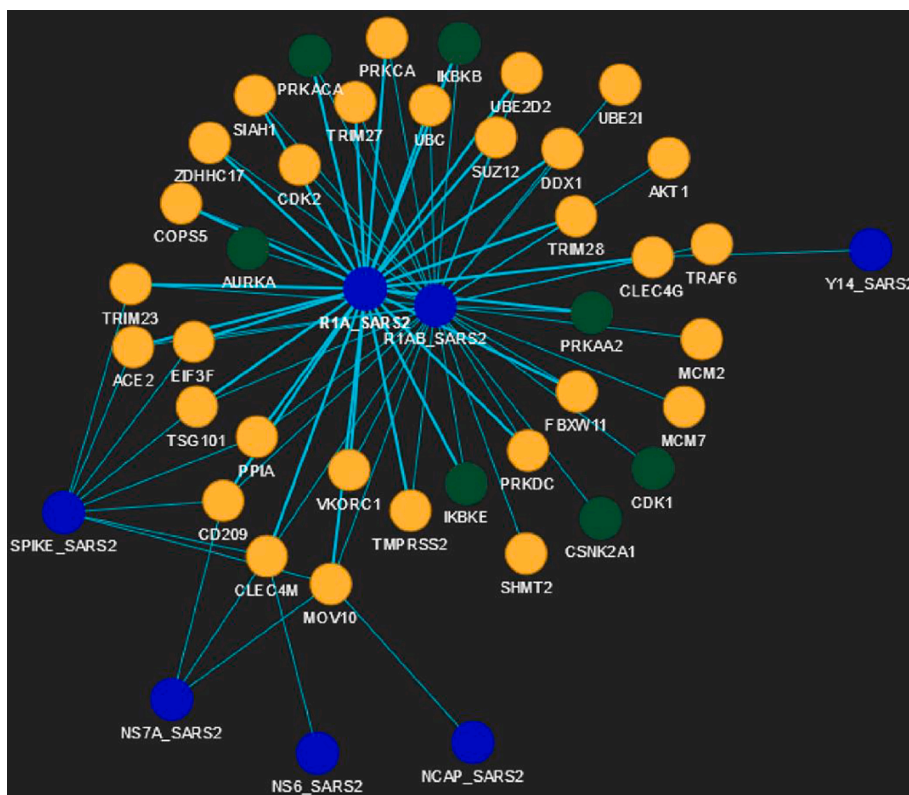


Fig. 4. Application of PDS_CS algorithm in Human-CoV PPIN (level-1). DCS score of Fostamatinib/R406 in level-1 is 7 (green nodes). Blue and yellow nodes denote COVID-19 and other level-1 proteins, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of occurrence. Similarly, for the symptom “loss of smell”, 12 overlapping genes are detected, mapping which with known drug targets in DrugBank has also been done (see [supplementary Table S5](#)). After applying the PDS_CS algorithm, only Fostamatinib/R406 and copper emerge based on their frequency of occurrence.

3.3. Docking results for potential COVID-19 drugs with respect to COVID-19 protein structures

Molecular docking is used in the proposed methodology to measure the binding capability of the potential COVID-19 drugs on 6LU7, 6M2Q, 6W9C, 6M0J, 6M71 and 6VXX. The detailed procedure of execution has been already discussed in the methodology section. In this work, SDF/PDB format is used for the docking of all the COVID-19 drugs. The results of docking with 6LU7 are highlighted in the [supplementary Table S6](#). At the same time, docking results with others are shown in [Table 5](#) and [Table 6](#). It is observed from the results that while Fostamatinib/R406 registers the highest score for 6LU7 and 6M2Q, it obtains the second position in comparison to the other COVID-19 structures.

3.4. Docking results for active metabolites/promoieties of COVID-19 Prodrugs with respect to COVID-19 protein structures

Several drug molecules consist of pharmacologically inactive compounds, which are known as Prodrugs [70]. These drugs get metabolized after entering the human body to liberate the active drug. On careful observation, it has been observed that Fostamatinib is also a prodrug. Fostamatinib (R788) is considered to be an orally induced prodrug in humans that releases active metabolite/promoiety R940406 (R406) [71]. R406 is a spleen tyrosine kinase (SYK) inhibitor responsible for treating rheumatoid arthritis [71]. Similar instances have also been observed in the case of remdesivir and favipiravir. So, the binding

capability of these active metabolites/promoieties must be validated against 6LU7, 6M2Q, 6W9C, 6M0J, 6M71 and 6VXX by molecular docking for consideration of any prodrug as a COVID-19 drug. The results of this docking with 6LU7 are highlighted in the [supplementary Table S7](#). At the same time, docking results with others are shown in [Table 7](#) and [Table 8](#). The result draws the reference that R406 also shows high binding affinity scores compared to the others, which promotes the fact that Fostamatinib/R406 can be a potential COVID-19 drug. Molecular docking results of Fostamatinib and its corresponding promoiety, R406, have also been highlighted in [Fig. 6](#).

3.5. Analysis of 3 key target genes of Fostamatinib/R406 in Human-nCoV interaction network in symptom-based analysis

The three key target genes of Fostamatinib/R406, as identified in the [supplementary Table S3](#) and [Table S4](#), are CDK1 (level-1) and NTRK1, EGFR (level-2). It is noted that these three genes are related to the most significant COVID-19 symptoms, risk factors and clinical outcomes, which are highlighted in [Table 9](#). Moreover, these three genes also play an essential role in response to viral infections which has been highlighted in [Table 10](#). All these depict the fact that Fostamatinib/R406 might be a potential drug treatment to COVID-19 treatment.

3.6. Application of algorithm S1 (PDS_CS) on in the host targets of in vitro generated Human-nCoV PPIN of Gordon et al. [13]

Gordon et al. [13] cloned, tagged, and expressed 26 of the 29 SARS-CoV-2 proteins in human cells and identified the human proteins that are physically associated with each of the SARS-CoV-2 proteins by affinity-purification mass spectrometry. As a result, 332 high-confidence protein–protein interactions between SARS-CoV-2 and human proteins are identified. These 332 host targets are collected, and Algorithm 1

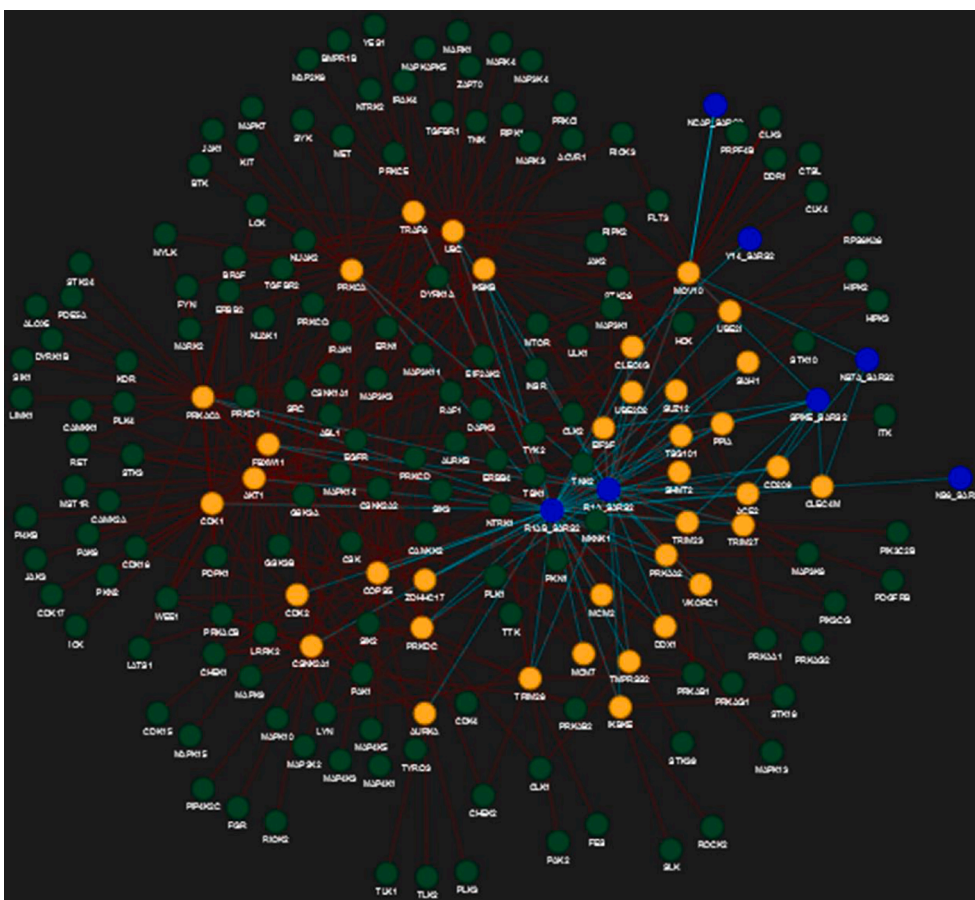


Fig. 5. Application of PDS_CS algorithm in Human-CoV PPIN (level-2). DCS score of Fostamatinib/R406 in level-2 is 148 (green nodes). Blue and yellow nodes denote COVID-19 and other level-1 spreader proteins, respectively. Other level-2 spreaders are not shown to avoid visual complexity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 5

Docking scores (Moldock Score) of drugs for 6VXX, 6M71, 6M2Q, 6W9C, 6M0J.

Drugs	Drug ID	Moldock score (6VXX)	Moldock score (6M71)	Moldock score (6M2Q)	Moldock score (6W9C)	Moldock score (6M0J)
Ritonavir	DB00503	-228.318	-201.076	-121.515	-230.852	-197.609
Fostamatinib	DB12010	-172.859	-179.834	-120.397	-185.156	-176.483
Lopinavir	DB01601	-166.217	-166.388	-114.563	-181.474	-170.136
Remdesivir	DB14761	-152.678	-160.739	-112.938	-172.778	-165.157
Darunavir	DB01264	-144.579	-152.622	-90.9735	-156.453	-152.907
Hydroxychloroquine	DB01611	-127.194	-110.183	-80.4403	-132.054	-122.721
Azithromycin	DB00207	-120.155	-105.759	-66.3967	-127.711	-115.321
Favipiravir	DB12466	-76.41	-73.7678	-14.436	-72.6467	-70.8629

Table 6

Docking scores (Rerank Score) of drugs with for 6VXX, 6M71, 6M2Q, 6W9C, 6M0J.

Drugs	Drug ID	Rerank Score (6VXX)	Rerank Score (6 M71)	Rerank Score (6M2Q)	Rerank Score (6W9C)	Rerank Score (6M0J)
Ritonavir	DB00503	-154.226	-140.533	-92.2327	-160.902	-130.098
Fostamatinib	DB12010	-57.5164	-110.545	-87.5182	-130.02	-130.509
Lopinavir	DB01601	-81.6619	-138.449	12.9996	-147.683	-125.165
Remdesivir	DB14761	-101.76	-124.925	-84.1368	-108.703	-119.626
Darunavir	DB01264	-103.522	-122.378	-66.1872	-115.516	-73.643
Hydroxychloroquine	DB01611	-100.612	-88.6121	18.5798	-102.419	-97.8097
Azithromycin	DB00207	-88.4657	-72.8345	-54.8591	-100.182	-31.7329
Favipiravir	DB12466	-62.055	-52.7567	793.471	-59.1369	-57.8456

(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 Table 11.

The ten host target genes associated with Fostamatinib/R406 in Table 11 are TBK1, CIT, NEK9, RIPK1, COQ8B, CSNK2A2, MARK1,

Table 7

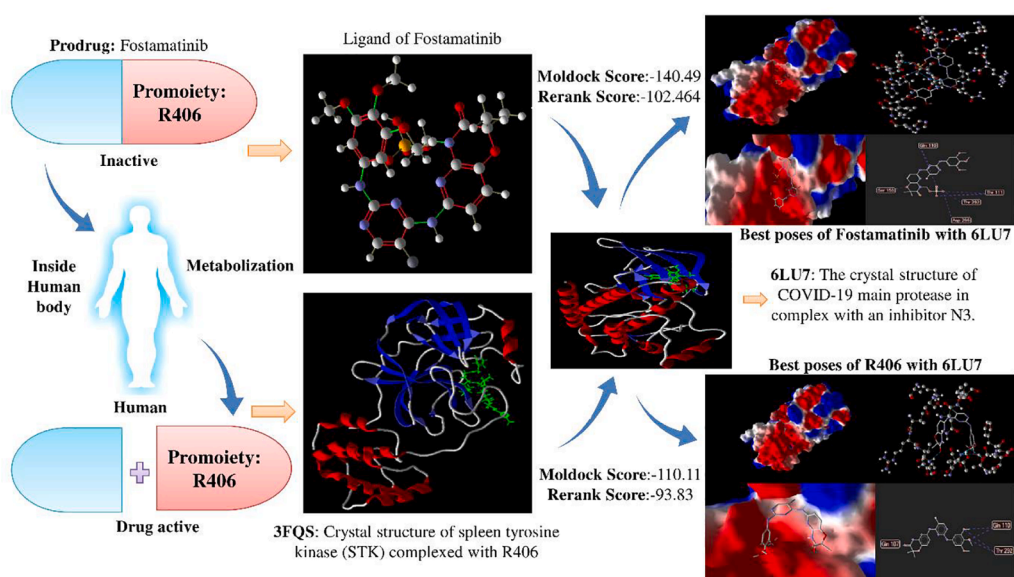
Docking scores (Moldock Score) of Prodrugs for 6VXX, 6M71, 6M2Q, 6W9C, 6M0J.

Prodrugs	Drug id	Active promoieties	Moldock Score (6VXX)	Moldock Score (6M71)	Moldock Score (6M2Q)	Moldock Score (6W9C)	Moldock Score (6M0J)
Fostamatinib	DB12010	RP406 (using 3FQS)	-143.34	-131.064	-115.229	-150.184	-134.057
Remdesivir	DB14761	GS-441524	-115.54	-106.624	-106.108	-107.333	-120.417
Favipiravir	DB12466	RdRp complex (6K32)	-92.5709	-100.143	-54.3239	-93.9083	-71.9692

Table 8

Docking scores (Rerank Score) of Prodrugs for 6VXX, 6M71, 6M2Q, 6W9C.

Prodrugs	Drug id	Active promoieties	Rerank Score (6VXX)	Rerank Score (6M71)	Rerank Score (6M2Q)	Rerank Score (6W9C)	Rerank Score (6M0J)
Fostamatinib	DB12010	RP406 (using 3FQS)	-115.106	-109.152	-76.3059	-111.853	-111.887
Remdesivir	DB14761	GS-441524	-91.7647	-80.5349	-70.1108	-87.910	-94.3608
Favipiravir	DB12466	RdRp complex (6K32)	-66.4667	-84.9671	-49.3377	-81.8392	-57.9054

**Fig. 6.** 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 COVID-19 drugs.**Table 9**

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
		Level-2	fever	–	kidney disease cancer
	EGFR	Level-1	pneumonia	neutrophilia	hypertension lung disease diabetes
		Level-2	pneumonia	kidney injury thrombocytopenia	heart disease hypertension cancer kidney disease lung disease diabetes

MARK3, MARK2 and PRKACA. In addition, on careful observation, it has been noted that these genes also play an essential role in response to viral infections, which has been discussed below:

- TBK1:** TBK1 (TANK-binding kinase 1) plays a highly significant role in developing natural immunity against antiviral activities. It activates IRF (interferon regulatory factor) 3, which in turn induce type I

Table 10
Role of CDK1 and NTRK1, EGFR in viral infections.

Drug	Key Target Genes	Level	Role in viral infections
Fostamatinib	CDK1	Level-1	Viruses can express some oncoproteins. Genome replication gets induced inside the hosts' cells due to some signals generated due to the interference of these proteins with CDK and CKs function [70].
	NTRK1	Level-2	NTRK1 has an active role in the immune response against viral infection [71].
	EGFR	Level-2	Hindrance of EGFR signalling might prevent an excessive fibrotic response to SARS-CoV.

Table 11
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

interferon (IFNs) (IFN- α/β) proteins regulating immune activity [72].

- CIT:** Encoded serine/threonine protein kinases are unique features in a specific set of giant DNA viruses. However, their role in the replication of virus varies. But different viral serine/ CIT (Citron Rho-Interacting Serine/Threonine Kinase) has the potentiality to act as the targets of antiviral drugs [17].
- NEK9:** Nek9 exhaustion leads to the reduction of virus replication centres within which it remains confined. However, Nek9 over-expression will increase the number of viral genomes in the infected cell [73].
- RIPK1:** Enhancement of plasma pro-inflammatory cytokines and lymphopenia is considered to be one of the significant predictors in increasing COVID-19 severity. Activating RIPK1 promotes the growth of these cytokines. In addition, it leads to the exhaustion of T cell populations (lymphopenia) in patients who get infected with HIV, which might pave the way for the entrance of SARS-CoV-2 in them [74].
- COQ8B:** Mitochondrial metabolism is executed as a part of the metabolic pathway through the interaction of SARS-CoV-2's M protein and COQ8B [75].
- CSNK2A2:** CSNK2A2 is involved in the regulation of primary cellular processes as well as viral infection [76].
- MARK1:** MARK1 plays an active role in viral responses [77].
- MARK2:** MARK2 is engaged in stimulating FEZ1 (Fasciculation And Elongation Protein Zeta 1) phosphorylation on the central cores of viruses [80].
- PRKACA:** PRKACA also plays a similar role in cardiovascular disease as that of MARK3 [78,81].

4. 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/R406, an FDA approved drug, as the most promising drug with the best chances to target the COVID-19 spreader proteins. The work relies on the hypothesis that SARS-CoV2/nCoV has ~89% genetic resemblance with SARS-CoV. Based on this, Human-nCoV PPIN has been developed, and its spreader nodes have been identified using the SIS model and fuzzy

thresholding. Furthermore, 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/R406 are highest in analysing the candidate drugs for COVID-19 spreader proteins. Besides, Fostamatinib/R406 also generates satisfactory results in molecular docking with the available COVID-19 protein structures. It also targets CAYP34A [23,82], a common target for almost all the FDA approved drugs [15] for COVID-19. Moreover, recent studies also suggest that it is used for thrombocytopenia [23] which is also associated with severe coronavirus disease 2019 (COVID-19) infections [24].

A clinical test is needed as the FDA approves Fostamatinib/R406 in immune thrombocytopenia [83] and to determine its efficacy against SARS-CoV2. Rigel pharmaceuticals have already started the clinical trials of Fostamatinib/R406 [29]. The results obtained are quite encouraging and positive regarding reports published to date [27,83]. According to the reports [27,83], Fostamatinib meets the "primary endpoint of Safety in Phase 2 Clinical Trial" conducted in hospitalized patients affected with COVID-19. In addition to this, they have also enrolled themselves for Phase 3 clinical trial of fostamatinib/R406 to treat the same. But arriving at a specific conclusion needs time and more research analysis. In a nutshell, our computational research evidence discovers that Fostamatinib/R406 may be considered one of the strong contenders for COVID-19 treatment.

CRedit authorship contribution statement

Sovan Saha: Conceptualization, Data curation, Methodology, Writing - original draft, Software. **Anup Kumar Halder:** Conceptualization, Data curation, Methodology, Writing - original draft, Software. **Soumyendu Sekhar Bandyopadhyay:** Data curation, Writing - original draft, Visualization. **Piyali Chatterjee:** Supervision, Investigation, Formal analysis, Writing - review & editing. **Mita Nasipuri:** Supervision, Project administration, Investigation, Formal analysis, Writing - review & editing. **Debdas Bose:** Formal analysis, Validation. **Subhadip Basu:** Supervision, Project administration, Investigation, Formal analysis, Data curation, Methodology, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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