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Proteomics advances towards developing SARS-CoV-2 therapeutics using *in silico* drug repurposing approaches

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Standing amidst the COVID-19 pandemic, we have faced major medical and economic crisis in recent times which remains to be an unresolved issue till date. Although the scientific community has made significant progress towards diagnosis and understanding the disease; however, effective therapeutics are still lacking. Several omics-based studies, especially proteomics and interactomics, have contributed significantly in terms of identifying biomarker panels that can potentially be used for the disease prognosis. This has also paved the way to identify the targets for drug repurposing as a therapeutic alternative. US Food and Drug Administration (FDA) has set in motion more than 500 drug development programs on an emergency basis, most of them are focusing on repurposed drugs. Remdesivir is one such success of a robust and quick drug repurposing approach. The advancements in omics-based technologies has allowed to explore altered host proteins, which were earlier restricted to only SARS-CoV-2 protein signatures. In this article, we have reviewed major contributions of proteomics and interactomics techniques towards identifying therapeutic targets for COVID-19. Furthermore, *in-silico* molecular docking approaches to streamline potential drug candidates are also discussed.

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Introduction

The Coronavirus disease (2019) had emerged as an unfortunate outbreak in December 2019, and by earlier months of 2020, it had turned into a worldwide pandemic. Nowadays, the disease is spreading faster than we ever imagined along with its mutated variants. Since the time of outbreak, it was

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thought to be a pneumonia-like disease or dyspnea which affects the lung and the respiratory organs [1], however, today we can imagine COVID-19 to be more of an inflammatory disease, especially affecting the cardiovascular condition [2]. Despite the large amount of research that has been done in the field of SARS-CoV-2 therapeutics, we are still struggling to come up with a definitive cure.

High-throughput technologies such as proteomics and interactomics have paced up to search for effective solutions. These omics-based investigations allow the holistic characterization of the proteins to compare the protein expression profiles in diseased versus normal conditions at the systems level, which uncovers the underlying molecular pathways associated with the pathophysiology of the disease. This provides a strong biological basis for the identification of targets for therapeutic intervention using proteomics. For a latest instance, in the light of current SARS-CoV-2 outbreak, proteomics studies have vastly contributed to the understanding of viral pathogenesis and host response, identifying some major cellular pathways that get dysregulated in response to infection [3].

In the field of pharmacotherapy, *in-silico* drug repurposing approaches have gained considerable momentum lately. It gradually happened due to the commercially viable strategy of computational approaches and the struggles of making a proper vaccine candidate for RNA viruses like SARS-CoV-2. US food and drug administration (FDA) has started Coronavirus Treatment Acceleration Program or CTAP [4], where it includes multiple drug development schemes and drug trials. In October 2020, Remdesvir [5] (a repurposed drug) was approved for the treatment of COVID-19 patients. With immense support of WHO, NIH, and other US federal agencies, several clinical trials are on-going with repurposed drugs (Table 1). Successful clinical trials are key to bringing new drugs to the masses in order to cope with the gruelling pandemic situation.

In this article, we have discussed the contributions of proteomics and interactomics towards identifying the dysregulated pathways underlying the pathophysiology of the disease. These pathways and the respective candidate proteins possess immense importance because they may serve as a target for future therapeutics and drug development. We have also critically analysed strategies that have been used in the field of *in silico* drug repurposing for SARS-CoV-2, what are the major outcomes till now, and discussed how far it can be improved.

Proteomics and Interactomics in identifying new targets for *in-silico* molecular docking

Evidently, most diseased conditions are manifested at the protein level. Moreover, the vast majority of pharmacologically active compounds bring about their action by binding to, and modulating the function of proteins [6]. Thus, proteins comprise the major class of target candidates amenable to pharmacological modulation for therapeutic purposes. They have been instrumental in revealing some major classifiers of COVID-19 infection including but not limited to inflammatory mediators, coagulation factors, acute phase proteins, apolipoproteins, cell adhesion proteins, and complement factors [7,8]. Multiple proteomics-based studies have revealed that dysregulation of proteins involved in neutrophil degranulation and blood coagulation is associated with COVID-19 disease severity [8–10]. Liu et al. showed that dipyridamole, an FDA-approved drug and an inhibitor of platelet aggregation and neutrophil extracellular trap (NET) formation [11,12], markedly improved clinical outcomes in severely ill patients [13]. Similarly, other FDA-approved anti-inflammatory drugs like anakinra (NCT04603742) and colchicine (NCT04326790) are undergoing clinical trials, since COVID-19 is characterized by a hyper-inflammatory state [14,15]. Thus, global proteome analysis not only serves to identify predictive biomarkers for disease severity and mortality, but also therapeutic targets for the effective disease mitigation (Fig. 1).

Unique proteome signatures in response to drug treatment can be compared to that of diseased phenotypes in order to identify overlapping proteins and pathways. Li et al. used label-based quantitative proteomics to study the proteome signature in response to ivermectin, a broad-spectrum anti-parasitic drug [16]. Their results indicated that several proteins dysregulated in response to SARS-CoV-2 infection [17] are included in ivermectin-regulated pathways, thereby suggesting ivermectin as a treatment option. Ivermectin has shown to inhibit SARS-CoV-2 *in vitro* [18] and is currently undergoing clinical trials for the treatment of COVID-19 (NCT04668469) [19]. Proteome analysis of virus-infected cell-line models can also give insights about host perturbations contributing to infection, thereby revealing probable targets for drug repurposing. One such study identified core cellular pathways that were affected due to SARS-CoV-2 infection and assessed the effect of few drugs targeting those pathways on viral inhibition [17]. The study identified and reported inhibition of SARS-CoV-2 by ribavirin (an inhibitor of nucleotide synthesis and an antiviral drug) and 2-deoxy-D-glucose (an inhibitor of carbon metabolism and an anti-cancer drug), both of which are undergoing clinical trials (NCT04494399, CTRI/2020/06/025664) [20,21]. In another study, Bouhaddou et al. investigated the phosphoproteome of SARS-CoV-2 infection in a cell line model and mapped the changes in phosphorylation patterns to disrupted kinases and pathways [22]. They identified a number of drugs at different stages of clinical development for prioritization and tested them for their antiviral activity. Thus, *in-vitro* infection models serve as a rapid means for some preliminary work to identify host factors involved in infection. Although such experimental proteomics studies can be set-up quickly and

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Table 1. *In-silico* studies for COVID-19.

In-silico studies for COVID-19

Drug	Current treatment	FDA status	Protein inhibited	Ref.	*In-silico* approach
Remdesivir	Ebola virus, Respiratory syncytial virus	Approved	RdRp	[30,56–58]	Phylogenetic analysis, structural and molecular docking, MD simulation, ensemble generation, homology modeling
Lopinavir–Ritonavir	HIV	Phase 2 clinical trials	Main Protease	[59–61]	Phylogenetic analysis, molecular docking, MD simulation
Ivermectin	Parasite infestation	Phase 3 clinical trials	RdRp	[62,63]	Molecular docking, MD simulation, MM-GBSA calculations
Ribavirin	Hepatitis C	Phase 2 clinical trial	RdRp	[34,64,65]	Sequence alignment, modelling, molecular docking, drug-likeness and bioactivity prediction, ADMET analysis
Indinavir	HIV	–	$3CL^{PRO}$ Main Protease.	[30,58]	Molecular docking, homology modelling
Lurasidone	Schizophrenia	–	Main Protease	[66,67]	Molecular docking and virtual screening, drug-likeness and bioactivity prediction, ADMET analysis, MD simulation, binding free energy calculation, P-L interaction energy calculation
Zanamivir	Influenza viruses	–	$3CL^{PRO}$Main Protease.	[68,69]	Molecular docking, homology modelling
Sofosbuvir	Hepatitis C	Phase 2	RdRp	[70,68]	Sequence alignment and modelling, molecular docking
Tenofovir	HIV	–	RdRp	[70,68]	Sequence alignment and modelling, molecular docking
Nelfinavir	HIV	–	Main Protease	[71–74]	Sitemap analysis, molecular docking and virtual screening, MD simulation, MM-GBSA calculations
Methisazone	Smallpox virus	–	5R80	[68]	Molecular docking
Saquinavir	HIV	–	Main protease	[68]	Molecular docking
Aclarubicin	Anti-cancer	–	Spike glycoprotein	[75,76]	Molecular docking and virtual screening, consensus scoring, MD simulation, MM-GBSA calculation
Galidesivir	Ebola virus	Phase 1	RdRp	[68,70]	Sequence alignment and modelling, molecular docking
Paritaprevir	Hepatitis C	–	Main Protease	[68]	Molecular docking and virtual screening
Selinexor	Anti-cancer	Phase 2	$3CL^{PRO}$ Main Protease.	[77,78]	Deep learning-based Drug Target Interaction (DTI) modelling
Neomycin	Aantibiotic	–	$3CL^{PRO}$ Main Protease.	[78]	MSM analysis, ensemble docking

Federally funded Clinical Studies

a. Ongoing (active) Phase 3 trials

Treatment	Trial identifier Number	Number of Participants	Experimental	Placebo	Actual Study Start Date	Estimated Study Completion Date	phase	Current therapeutic class
Remdesivir	NCT04492475	969	200 mg of Remdesivir administered intravenously on Day 1, followed by a 100 mg once-daily maintenance dose of Remdesivir while hospitalised for up to a 10-day total course and 44 mcg of interferon beta-1a administered by a 0.5 mL subcutaneous injection on Days 1, 3, 5, and 7 while hospitalized for a total of 4 doses.	200 mg of Remdesivir administered intravenously on Day 1, followed by a 100 mg once-daily maintenance dose of Remdesivir while hospitalised for up to a 10-day total course and a 0.5 mL placebo injection administered subcutaneously on Days 1, 3, 5, and 7 while hospitalised for a total of 4 doses.	August 4, 2020	December 30, 2020	3	Broad Spectrum Antiviral agent [79]

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Table 1 (*Continued*)

Federally funded Clinical Studies

a. Ongoing (active) Phase 3 trials

Treatment	Trial identifier Number	Number of Participants	Experimental	Placebo	Actual Study Start Date	Estimated Study Completion Date	phase	Current therapeutic class
LY3819253 + Remdesivir (Provided to all study participants as SOC unless contraindicated for an individual patient.)	NCT04501978	10,000	LY3819253 administered by IV infusion. Remdesivir provided to all as SOC.	Commercially available 0.9% sodium chloride solution. Remdesivir provided to all as SOC.	August 4, 2020	July 2021	3	Monoclonal Antibody [80]
mRNA-1273	NCT04470427	30,000	One intramuscular (IM) injection of 100 microgram (ug) mRNA-1273 on Day 1 and on Day 29.	One IM injection of 0.9% sodium chloride (normal saline) injection on Day 1 and on Day 29.	July 27, 2020	October 27, 2022	3	Lipid nanoparticle–encapsulated mRNA-based vaccine [81]
Remestemcel-L	NCT04371393	223	Intravenous infusion of remestemcel-L 2 × 10^6 MSC/kg of body weight plus standard of care. Administered twice during the first week, with the second infusion at four days following the first injection (± 1 day).	Placebo (Plasma-Lyte) plus standard of care. Administered twice during the first week, with second infusion at 4 days following the first injection (± 1 day).	April 30, 2020	February 2022	3	Allogeneic Human Mesenchymal Stem Cell Therapy [82]

b. Completed trials (All Phases)

Treatment	Trial identifier Number	Number of Participants	Experimental conditions	Placebo	Actual Study Start Date	Estimated Study Completion Date	Phase	
Remdesivir + Baricitinib	NCT04401579	1034	200 mg of Remdesivir administered intravenously on Day 1, followed by a 100 mg once-daily maintenance dose of Remdesivir while hospitalized for up to a 10-day total course and 4 mg (2 tablets of 2 mg) of Baricitinib administered orally daily for the duration of the hospitalisation up to a 14-day complete course.	Baricitinib Placebo: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate	May 8, 2020	July 31, 2020	3	Broad Spectrum Antiviral agent [79]
Remdesivir	NCT04280705	1062	200 mg of formulation of Remdesivir and inactive ingredients administered intravenously on Day 1, followed by a 100 mg once-daily maintenance dose of Remdesivir while hospitalized for up to a 10 days total course. n = 286.	Formulation only with the inactive ingredients: water for injection, sulfobutylether beta-cyclodextrin sodium (SBECD), and HCl and/or NaOH	February 21, 2020	May 21, 2020	3	Broad Spectrum Antiviral agent [79]

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Table 1 (*Continued*)

b. Completed trials (All Phases)

Treatment	Trial identifier Number	Number of Participants	Experimental conditions	Placebo	Actual Study Start Date	Estimated Study Completion Date	Phase	
Hydroxychloroquine (HCQ) + Azithromycin (Azithro)	NCT04358068	20	HCQ 400 mg (administered as two 200 mg capsules) orally twice daily for 2 doses starting on Day 0, followed by 200 mg (administered as one 200 mg capsule) twice daily for 12 doses (6 days), PLUS: Azithromycin 500 mg (administered as two 250 mg capsules) orally as a single dose on Day 0, followed by 250 mg (administered as one 250 mg capsule) orally once daily for 4 doses (4 days).	Placebo for HCQ as well as Azithro	May 1, 2020	July 7, 2020	2	Antimalarial Drug [83]
L-ascorbic acid (Vitamin C)	NCT04357782 [a]	20	Mild hypoxemia: 50 mg/kg L-ascorbic acid infusion given every 6 hours for four days	Severe hypoxemia: 50 mg/kg L-ascorbic acid infusion given every 6 hours for four days	April 16, 2020	October 13, 2020	2	Used to treat melasma [84]
Hydroxychloroquine (HCQ)	NCT04332991	479	An oral or enteral dose of hydroxychloroquine 400 mg twice daily on the day of enrollment, then 200 mg twice daily for the next four days	Placebo for HCQ	April 2, 2020	July 23, 2020	3	Antimalarial Drug [83]

[a] This study is a comparison between mild and severe hypoxemia patients (mild: S/F ratio$>$ 250, severe: S/F ratio $\leq$ 250, both prior to Vitamin C infusion).

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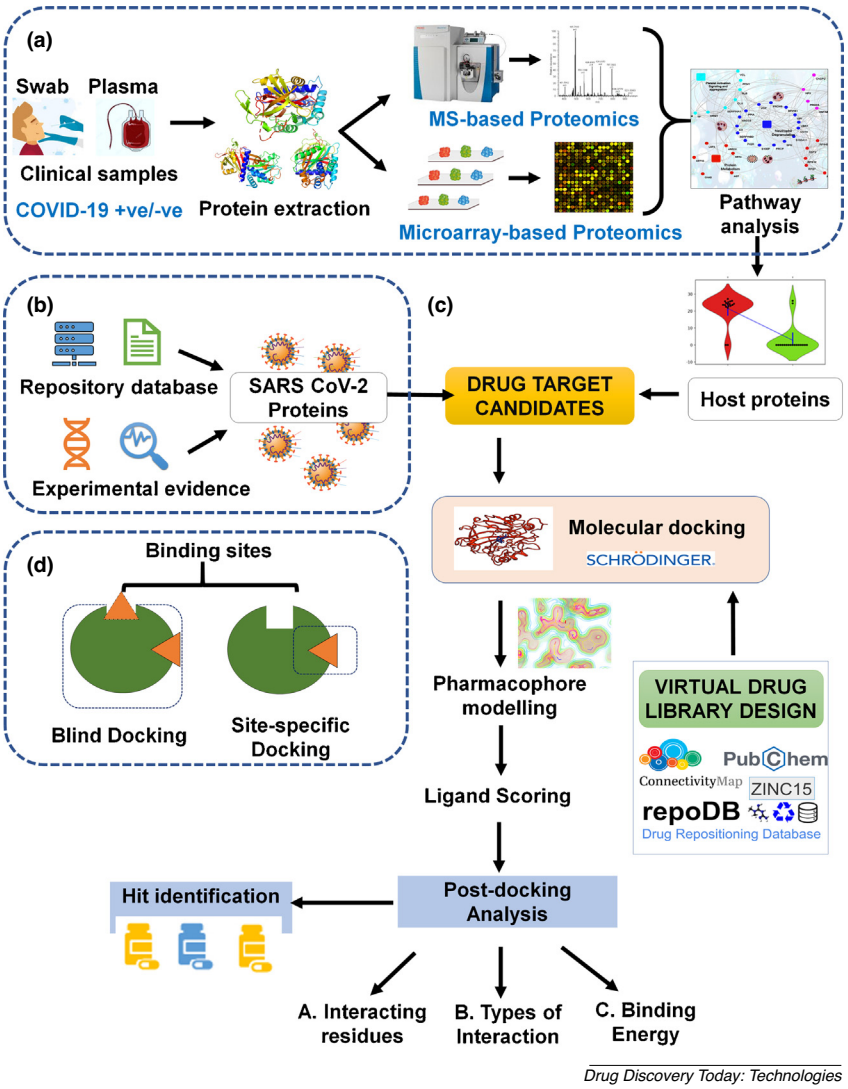

Fig. 1. Represents the drug repurposing strategy directly translated from omics-based techniques. A. Different proteomics approaches used to identify host target proteins; B. Experimental evidences and repository databases help to shortlist viral proteins; C. Basic strategies used in literature for *In-silico* molecular docking and screening of potential drug candidates. D. Types of *in-silico* molecular docking: blind and site-specific docking.

require minimal ethical clearance, they have their limitations since in-vitro models cannot truly mimic the systemic body. Regardless, it is a worthwhile practice to prioritize leads and set the ground for future research.

It is given that the virus utilizes host machinery to carry out its life processes and achieve the associated pathophysiology. For that matter, the viral components must physically interact with the host components and interfere with the cellular pathways. Protein interactomics is a discipline that seeks to characterize the interactions between and among proteins. The protein-protein interaction (PPI) networks can aid in the identification of some potent therapeutic targets [23] as disruption of intra-viral or virus-host PPIs indispensable to the viral life cycle presents an attractive strategy to prevent infection. Gordon et al. characterized the SARS-CoV-2 virus-host PPI network by affinity-purification mass spectrometry that further led to the identification of targets for drug repurposing [24]. Sadegh et al. have developed an online platform, 'CoVex' for SARS-CoV-2, which integrates virus-human PPI, human PPI and drug-target interaction for the identification of the drug candidates for therapeutics [25]. Interactomics, therefore, is an appealing strategy to decipher disease mechanisms and identify targets for drug repurposing. However, it is not devoid of limitations as the experimental design is not a true representative of the physiological conditions. Hence, it becomes imperative to confirm the functional importance of the PPIs. Nevertheless, interactomics offers a powerful resource to streamline the target identification regime for drug repurposing. The major proteomics approaches discussed here are depicted in Fig. 2A.

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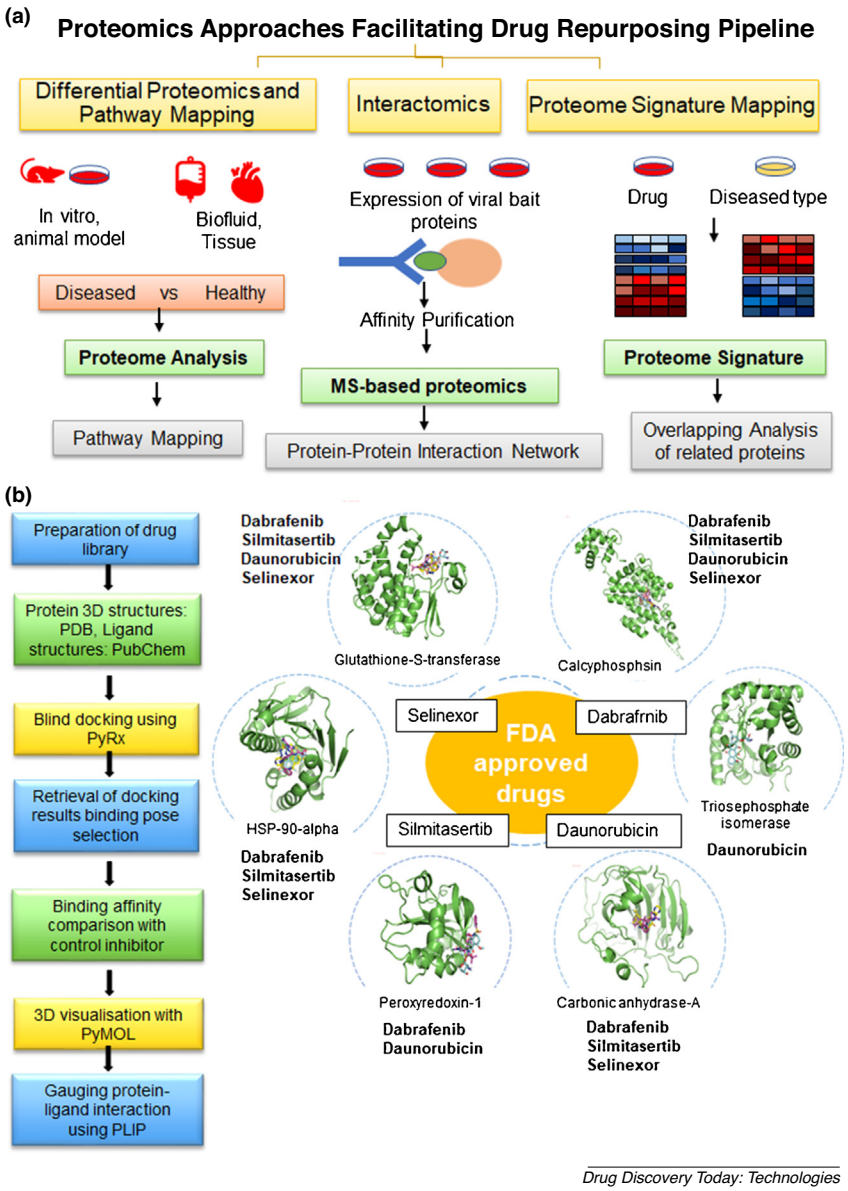

Fig. 2. a. Major proteomics-based approaches to identify potential therapeutic targets for drug repurposing; b. depicts the software pipeline adopted by our group to perform molecular docking of potential drug targets (differentially expressed proteins); C is a representative image of molecular docking results using 4 FDA approved drugs on 6 different proteins.

Current studies of *in-silico* drug repurposing against SARS-CoV-2

Viral protein driven in-silico *drug repurposing*

Current studies in SARS-CoV-2 involve targeting a few selected viral proteins that play major roles in viral replication and entry. The Mpro or main protease is one of the best-characterized drug targets so far [26]. Mpro cleaves the poly-proteins into active viral proteins produced by viral RNA and hence is a very important candidate for viral replication [27], so blocking the catalytic activity of this protein can give us satisfying results in terms of reducing the viral load. Various natural compounds and few FDA-approved drugs were screened for Mpro in different studies across the globe and it was found that small molecules such as EGCG [27], Lopinavir–Ritonavir [28], Selinexor [29], Indinavir [30], Nelfinavir [31] and Saquinavir [32]. Few of the drugs such as Indinavir Nelfinavir and Saquinavir have been previously used for HIV treatments (Table 1). Another study has shown some synthetic analogs of flavonoids, especially, thio flavonols, can inhibit the catalytic activity of Mpro [33]. Another example of viral protein driven drug development includes the RNA-dependent RNA polymerase (RdRp) protein. RdRp is responsible for RNA replication and plays a key role in the viral life cycle, thus making it an attractive drug target. Molecular docking studies show

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that a total of five FDA approved drugs such as, Remdesivir, Sofosbuvir, Galidesivir, Tenofovir and Ribavirin bind tightly with RdRp [34], claiming the fact that these drugs can be used against COVID-19. Among these potent antiviral drugs, Remdesivir has already been selected [5]. RdRp from SRS-CoV-2 shares 97% sequence identity [34] with previously emerged SARS, which makes the RdRp protein a great target for developing multi-strain repurposed drugs. Recently, a total of 4015 known and approved small molecules were screened against the spike glycoprotein (SARS-CoV-2-S) [35]. The importance of spike protein lies in the viral entry mechanism. It binds to the human ACE2 receptor with S1 subunit [36]. 15 top compounds were shortlisted including streptomycin, ciprofloxacin, and glycyrrhizic acid [35]. Both streptomycin and ciprofloxacin are originally antibacterial agents, but they have proven antiviral activities as well [35]. The ideal way to repurpose drugs in this case would be finding compounds that can target multiple viral proteins at once, increasing the efficacy of the drug to several folds.

Host protein driven in-silico *drug repurposing*

This section of drug repurposing strategy based on host proteins is slightly different. Post viral infection, proteome composition of various body fluids (plasma, serum) and secretory fluids (swab) changes abruptly. Few of these proteins, which are over-expressed, play a role in disease progression. We can target and inhibit such human proteins as a unique strategy of treatment. Such studies might make a bigger impact instead of targeting viral proteins keeping the fragile nature of RNA viruses in mind. These viruses undergo spontaneous mutations (approximately 1 per genome per replication), which is 300-fold higher than DNA-based microbes [37]. As a consequence, the protein sequences will alter, making the chosen therapeutics less impactful over a period of time. Both computational and biological experimental approaches are applied here. Host targets can be identified from a repository database such as gene expression, host proteome profiles, while keeping few constraints in mind such as drug-target interactions, toxicity database and several clinical trial reports. Secondly, group-specific omics-based clinical studies (proteomics, transcriptomics and metabolomics) can be performed and from these investigations overexpressed protein candidates from COVID-patients (mild, moderate and severe) can be used as target for drug repurposing studies. One such study included targeting host receptors (ACE2) as well as a specific host factor called angiotensin receptors AT1, AT2 [38]. Similarly, when a total of 26 SARS-CoV-2 proteins were cloned and expressed in human cells, 66 druggable host proteins were found to be inhibited by 29 FDA approved compounds by the chemoproteomic analysis [24]. The authors claimed, the strategy of host-directed intervention may overcome drug resistance issues and may come up with pan viral therapies for future pandemics.

COVID-19 drug repurposing: approaches and techniques

Molecular docking-based drug repurposing is a cost effective and rapid technique for the drug discovery process. There are multiple approaches that can be used to identify suitable drug candidates for a disease. The first step in a molecular docking experiment is to obtain the 3D structure of the target macromolecule. The structure can be easily retrieved from the Protein Data Bank (PDB) [39]. Many times the 3D structure of the target protein is not available and to overcome this issue computational prediction methods are used. To start the docking, ligand binding site should be known to calculate the binding energies. Sometimes when binding site location is not known, two methods are most commonly used: in one method algorithms are used to predict the most probable binding site and, in another approach, blind docking is performed [40]. In the blind docking approach, the entire target protein structure is considered as a binding site. Ligand's 3D structure can be downloaded from small molecules databases such as ZINC [41] and PubChem [42]. In the study performed by Bhumi Shah et al., for COVID 19 drug repurposing, they have extracted 3D structures of 61 reported antiviral agents from PubChem and created a library of ligands for molecular docking [43]. Several software can be used to perform molecular docking such as AutoDock [44], GOLD [45], DockThor [46,47] and MolDock [48]. In the post docking analysis, pose with minimum binding affinity is selected. Some molecular docking algorithms provide rankings to the docked ligands using the binding affinity of ligand receptor complex.

In order to identify the repurposed drugs which could be potential candidates for the treatment of SARS-CoV-2, the following procedure was undertaken by our research group (ref) (Fig. 2). Literature was extensively reviewed to find small molecule inhibitors of target proteins, which was used as control inhibitors during molecular docking. A drug library of 80+ small molecules was prepared. Protein structures were downloaded in .pdb format from PDB and a Python script was written for parsing the protein PDB files to select only ATOM lines in requisite chains. The 3D structures of all drug molecules were extracted from PubChem and OpenBabel was utilised for converting the 3D SDF files of drug molecules to PDBQT. Blind docking of the ligands to the proteins was performed using PyRx in order to check their binding affinity. Another Python script was crafted and executed for splitting the post-docking PDBQT files. The pose with the highest binding affinity was taken forward for further analysis. The drugs in the library that had more negative binding affinity than that of the control molecule were filtered out. Then, PyMOL was used for visualising the binding of these drugs.

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Those that had similar binding pockets as that of the control inhibitor were picked. Further analysis of the protein and drug interactions can be done through the online PLIP server which helps to identify various interactions of amino acids and drug molecules, which include hydrogen bond, ionic interactions, hydrophobic interactions, salt bridges, etc. The shortlisted drugs were then compared for various proteins to find some common drug(s) that can be chosen as a candidate for repurposing.

The procedure of *in-silico* drug repurposing mentioned earlier was applied on differentially expressed protein targets (which are found to be upregulated in COVID-19 patients) obtained from swab and plasma proteomes from patients using both shotgun and targeted proteomics [49,50]. Such target proteins include: Calcyphosin (Q13938), HSP 90-beta, HSP 90-alpha, Carbonic Anhydrase 2, Glutathione S-transferase P, Peroxiredoxin-1, Pyruvate kinase PKM, Triosephosphate isomerase. These proteins were docked against a customised drug library of 58 small molecules. It was observed that FDA approved drug Dabrafenib inhibited 5 out of 8 above mentioned differentially expressed proteins. Other 3 FDA approved drugs namely Silmitasertib, Selinexor, Daunorubicin were predicted to inhibit 4 out of 8 proteins. Other drugs in the list included CCT 365623 and ABBV-744 which are in the clinical trials; they were predicted to inhibit 5 out of 8 proteins. Illustration of such workflow (Figure-2 B and C) will provide readers a clear understanding of how drug repurposing studies could be performed.

Conclusions

The drug discovery and development process is a massive undertaking including multiple phases, extreme safety assessments, and extensive regulatory requirements. The estimated cost for a new drug to enter the market has more than doubled from already whopping USD $1 billion in early 2000's to USD $2.6 billion currently [51–53]. Moreover, it takes around 10–12 years or even more for a drug to reach to the market [54]. The escalating cost and time length for drug development together with other challenges faced by the pharmaceutical industry has made repurposing of existing drugs an attractive strategy. In the face of emerging infectious disease outbreaks, such as the current global pandemic of COVID-19 caused by the novel and highly infectious SARS-CoV-2, drug repurposing is a more feasible and practical approach to look for therapeutics than developing drug de *novo*.

One limitation of this approach is that since the drug repurposing approach mentioned in this review article is entirely based on *in-silico* molecular docking experiments, further validation experiments should be performed to confirm the antiviral efficacy of the identified repurposed drugs. Many times, it has been observed that the drugs identified in the *in-silico* experiments, failed to show similar efficacy in the *in vitro* experiments. When used with appropriate validation methods (molecular dynamic simulations or cell culture and animal model studies), the approach can effectively streamline drugs that can be further taken for clinical trials.

The advancements in the proteomics technologies, allow the high-throughput identification of proteins from complex biological samples. Given the multi-fold benefits of drug repurposing and technical advancements in proteomics techniques, there is widespread interest among researchers from varied fields towards incorporating proteomics and interactomics to the drug repurposing pipeline. We have discussed recent studies which have employed proteomics and interactomics to identify SARS-CoV-2 target proteins in a comprehensive manner.

One such study by Gordon et al. has employed interactomics to identify druggable human proteins which are found to be interacting with the SARS-CoV-2. They reported that 40% of the interacting host proteins are associated with endomembrane compartments or vesicle trafficking pathways thereby favouring SARS-CoV-2 replication [55]. This study indicates the role of host factors/proteins in the disease progression and hence they could be used as targets for drug repurposing. This approach is very practical where identified target proteins can be targeted by the already approved drugs. Proteomics and interactomics are very useful to uncover the potential drug targets and to explore the protein-protein interactions, which could ultimately increase the success of the drug repurposing program.

Conflict of interest

We declare that the content of this manuscript has not been copyrighted or published previously or is under review.

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References

[1] Wu F, Zhao S, Yu B, Chen YM, Wang W, Hu Y, et al. A new coronavirus associated with human respiratory disease in China. Nature 2020;579 (March (7798))7798. http://dx.doi.org/10.1038/s41586-020-2008-3.

[2] Unudurthi SD, Luthra P, Bose RJC, McCarthy JR, Kontaridis MI. Cardiac inflammation in COVID-19: lessons from heart failure. Life Sci 2020;260 (November):118482. http://dx.doi.org/10.1016/j.lfs.2020.118482.

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[3] Bojkova D, et al. Proteomics of SARS-CoV-2-infected host cells reveals therapy targets. Nature 2020;583(July (7816))7816. http://dx.doi.org/10.1038/s41586-020-2332-7.
[4] U. F. and D. Administration. Coronavirus treatment acceleration program (CTAP);FDA website 2020;p. 1–7.
[5] Bellera CL, et al. Can drug repurposing strategies be the solution to the COVID-19 crisis? Expert Opin Drug Discov 2020;(December):1–8. http://dx.doi.org/10.1080/17460441.2021.1863943.
[6] Hopkins AL, Groom CR. The druggable genome. Nat Rev Drug Discov 2002;1(9):727–30. http://dx.doi.org/10.1038/nrd892.
[7] Messner CB, et al. Ultra-high-throughput clinical proteomics reveals classifiers of COVID-19 infection. Cell Syst 2020;11(July (1)). http://dx.doi.org/10.1016/j.cels.2020.05.012. 11-24.e4.
[8] Shen B, et al. Proteomic and metabolomic characterization of COVID-19 patient sera. Cell 2020;182(July (1)). http://dx.doi.org/10.1016/j.cell.2020.05.032. 59–72.e15.
[9] Overmyer KA, et al. Large-scale multi-omic analysis of COVID-19 severity. Cell Syst 2020. http://dx.doi.org/10.1016/j.cels.2020.10.003.
[10] Li J, et al. Virus-host interactome and proteomic survey reveal potential virulence factors influencing SARS-CoV-2 pathogenesis. Med 2020. http://dx.doi.org/10.1016/j.medj.2020.07.002.
[11] Ali RA, et al. Adenosine receptor agonism protects against NETosis and thrombosis in antiphospholipid syndrome. Nat Commun 2019;10(1):1916. http://dx.doi.org/10.1038/s41467-019-09801-x.
[12] Gresele P, Momi S, Falcinelli E. Anti-platelet therapy: phosphodiesterase inhibitors. Br J Clin Pharmacol 2011;72(October (4)):634–46. http://dx.doi.org/10.1111/j.1365-2125.2011.04034.x.
[13] Liu X, et al. Potential therapeutic effects of dipyridamole in the severely ill patients with COVID-19. Acta Pharm Sin B 2020;10(7):1205–15. http://dx.doi.org/10.1016/j.apsb.2020.04.008.
[14] Huet T, et al. Anakinra for severe forms of COVID-19: a cohort study. Lancet Rheumatol 2020;2(July (7)):e393–400. http://dx.doi.org/10.1016/S2665-9913(20)30164-8.
[15] Schlesinger N, Firestein BL, Brunetti L. Colchicine in COVID-19: an old drug, new use. Curr Pharmacol Rep 2020;(July):1–9. http://dx.doi.org/10.1007/s40495-020-00225-6.
[16] Li N, Zhao L, Zhan X. Quantitative proteomics reveals a broad-spectrum antiviral property of ivermectin, benefiting for COVID-19 treatment. J Cell Physiol 2020;n/a(September). http://dx.doi.org/10.1002/jcp.30055.
[17] Bojkova D, et al. Proteomics of SARS-CoV-2-infected host cells reveals therapy targets. Nature 2020;583(7816):469–72. http://dx.doi.org/10.1038/s41586-020-2332-7.
[18] Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res 2020;178(June):104787. http://dx.doi.org/10.1016/j.antiviral.2020.104787.
[19] Ahmed S, et al. A five day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis)2020;(December). http://dx.doi.org/10.1016/j.ijid.2020.11.191.
[20] Hung IF-N, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet (London England) 2020;395(May (10238)):1695–704. http://dx.doi.org/10.1016/S0140-6736(20)31042-4.
[21] Verma A, Adhikary A, Woloschak G, Dwarakanath BS, Papineni RVL. A combinatorial approach of a polypharmacological adjuvant 2-deoxy-D-glucose with low dose radiation therapy to quell the cytokine storm in COVID-19 management. Int J Radiat Biol 2020;96(November (11)):1323–8. http://dx.doi.org/10.1080/09553002.2020.1818865.
[22] Bouhaddou M, et al. The global phosphorylation landscape of SARS-CoV-2 infection. Cell 2020;182(August (3)). http://dx.doi.org/10.1016/j.cell.2020.06.034. 685–712.e19.
[23] Feng S, Zhou L, Huang C, Xie K, Nice EC. Interactomics: toward protein function and regulation. Expert Rev Proteomics 2015;12(February (1)):37–60. http://dx.doi.org/10.1586/14789450.2015.1000870.
[24] Gordon DE, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature 2020;583(7816):459–68. http://dx.doi.org/10.1038/s41586-020-2286-9.
[25] Sadegh S, et al. Exploring the SARS-CoV-2 virus-host-drug interactome for drug repurposing. Nat Commun 2020;11(1):3518. http://dx.doi.org/10.1038/s41467-020-17189-2.
[26] Sharma S, Deep S. In-silico drug repurposing for targeting SARS-CoV-2 main protease (M(pro)). J Biomol Struct Dyn 2020;(November):1–8. http://dx.doi.org/10.1080/07391102.2020.1844058.
[27] Jin Z, et al. Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors. Nature 2020;582(7811):289–93. http://dx.doi.org/10.1038/s41586-020-2223-y.
[28] Kumar Y, Singh H, Patel CN. In silico prediction of potential inhibitors for the main protease of SARS-CoV-2 using molecular docking and dynamics simulation based drug-repurposing. J Infect Public Health 2020;13(9):1210–23. http://dx.doi.org/10.1016/j.jiph.2020.06.016.
[29] Anwar MU, et al. Combined deep learning and molecular docking simulations approach identifies potentially effective FDA approved drugs for repurposing against SARS-CoV-2. ChemRxiv 2020. http://dx.doi.org/10.26434/chemrxiv.12227363.v1.
[30] Hall Jr DC, Ji H-F. A search for medications to treat COVID-19 via in silico molecular docking models of the SARS-CoV-2 spike glycoprotein and 3CL protease. Travel Med Infect Dis 2020;35:101646. http://dx.doi.org/10.1016/j.tmaid.2020.101646.
[31] Mittal L, Kumari A, Srivastava M, Singh M, Asthana S. Identification of potential molecules against COVID-19 main protease through structure-guided virtual screening approach. J Biomol Struct Dyn 2020;(May):1–19. http://dx.doi.org/10.1080/07391102.2020.1768151.
[32] Farag A, et al. Identification of atovaquone, Ouabain and Mebendazole as FDA approved drugs tar-geting SARS-CoV-2 (Version 4); 2020.
[33] Batool F, et al. Synthetic flavonoids as potential antiviral agents against SARS-CoV-2 main protease. J Biomol Struct Dyn 2020;(November):1–12. http://dx.doi.org/10.1080/07391102.2020.1850359.
[34] Elfiky AA. Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): a molecular docking study. Life Sci 2020;253:117592. http://dx.doi.org/10.1016/j.lfs.2020.117592.
[35] Br B, Damle H, Ganju S, Damle L. In silico screening of known small molecules to bind ACE2 specific RBD on spike glycoprotein of SARS-CoV-2 for repurposing against COVID-19. F1000Research 2020;9(July):663. http://dx.doi.org/10.12688/f1000research.24143.1.
[36] Burkard C, et al. Coronavirus cell entry occurs through the endo-/Lysosomal pathway in a proteolysis-dependent manner. PLoS Pathog 2014;10(November (11))e1004502.
[37] Drake JW. Rates of spontaneous mutation among RNA viruses. Proc Natl Acad Sci U S A 1993;90(May (9)):4171–5. http://dx.doi.org/10.1073/pnas.90.9.4171.
[38] Goyal RK, et al. Current targets and drug candidates for prevention and treatment of SARS-CoV-2 (COVID-19) infection. Rev Cardiovasc Med 2020;21(September (3)):365–84. http://dx.doi.org/10.31083/j.rcm.2020.03.118.
[39] Berman HM, et al. The protein data bank. Nucleic Acids Res 2000;28(January (1)):235–42. http://dx.doi.org/10.1093/nar/28.1.235.
[40] Protein-Protein and Protein-Ligand Docking | IntechOpen.'' https://www.intechopen.com/books/protein-engineering-technology-and-application/protein-protein-and-protein-ligand-docking. [Accessed 24 April 2021].
[41] Irwin JJ, Shoichet BK. ZINC–a free database of commercially available compounds for virtual screening. J Chem Inf Model 2005;45(1):177–82. http://dx.doi.org/10.1021/ci049714+.
[42] Kim S, et al. PubChem substance and compound databases. Nucleic Acids Res 2016;44(January (D1)). http://dx.doi.org/10.1093/nar/gkv951. D1202-13.
[43] Shah B, Modi P, Sagar SR. In silico studies on therapeutic agents for COVID-19: drug repurposing approach. Life Sci 2020;252(July):117652. http://dx.doi.org/10.1016/j.lfs.2020.117652.
[44] Morris GM, et al. Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. J Comput Chem 1998;19(November (14)):1639–62. http://dx.doi.org/10.1002/(SICI)1096-987X(19981115)19:14<1639::AID-JCC10>3.0.CO;2-B.

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[45] Jones G, Willett P, Glen RC, Leach AR, Taylor R. Development and validation of a genetic algorithm for flexible docking. J Mol Biol 1997;267 (April (3)):727–48. http://dx.doi.org/10.1006/jmbi.1996.0897.
[46] de Magalhães CS, Barbosa HJC, Dardenne LE. Selection-insertion schemes in genetic algorithms for the flexible ligand docking problem. Genetic and evolutionary computation — GECCO 2004 2004;368–79.
[47] Magalhães C, Almeida DM, Barbosa H, Dardenne L. A dynamic niching genetic algorithm strategy for docking highly flexible ligands. Inf Sci 2014;289:206–24.
[48] Thomsen R, Christensen MH. MolDock: a new technique for high-accuracy molecular docking. J Med Chem 2006;49(June (11)):3315–21. http://dx.doi.org/10.1021/jm051197e.
[49] Suvarna K, et al. Proteomics and machine learning approaches reveal a set of prognostic markers for COVID-19 severity with drug re-purposing potential. Front Physiol 2021;12. http://dx.doi.org/10.3389/fphys.2021.652799.
[50] Bankar R, et al. Proteomic investigation reveals dominant alterations of neutrophil degranulation and mRNA translation pathways in patients with COVID-19. iScience 2021;24(March (3)):102135. http://dx.doi.org/10.1016/j.isci.2021.102135.
[51] Adams CP, Brantner VV. Estimating the cost of new drug development: is it really 802 million dollars? Health Aff 2006;25(2):420–8. http://dx.doi.org/10.1377/hlthaff.25.2.420.
[52] Morgan S, Grootendorst P, Lexchin J, Cunningham C, Greyson D. The cost of drug development: a systematic review. Health Policy 2011;100 (April (1)):4–17. http://dx.doi.org/10.1016/j.healthpol.2010.12.002.
[53] PhRMA. Prescription medicines: costs in context. Pharm Res Manuf Am 2016;(March):42.
[54] Torjesen Ingrid. Drug development: the journey of a medicine from lab to shelf. Pharm J 2015;1–5. URI:2008196.
[55] Gordon DE, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature 2020;583(July (7816))7816. http://dx.doi.org/10.1038/s41586-020-2286-9.
[56] Naik VR, et al. Remdesivir (GS-5734) as a therapeutic option of 2019-nCOV main protease — in silico approach. J Biomol Struct Dyn 2020;(June):1–14. http://dx.doi.org/10.1080/07391102.2020.1781694.
[57] Remdesivir-bound and ligand-free simulations reveal the probable mechanism of inhibiting the RNA dependent RNA polymerase of severe acute respiratory syndrome coronavirus 2 - RSC Advances (RSC Publishing).'' https://pubs.rsc.org/en/content/articlelanding/2020/ra/d0ra04743k#!divAbstract.
[58] Shah B, Modi P, Sagar SR. In silico studies on therapeutic agents for COVID-19: drug repurposing approach. Life Sci 2020;252(July):117652. http://dx.doi.org/10.1016/j.lfs.2020.117652.
[59] Kumar Y, Singh H, Patel CN. In silico prediction of potential inhibitors for the main protease of SARS-CoV-2 using molecular docking and dynamics simulation based drug-repurposing. J Infect Public Health 2020;13(September (9)):1210–23. http://dx.doi.org/10.1016/j.jiph.2020.06.016.
[60] Magro P, Zanella I, Pescarolo M, Castelli F, Quiros-Roldan E. Lopinavir/ritonavir: repurposing an old drug for HIV infection in COVID-19 treatment. Biomed J)2020;(November). http://dx.doi.org/10.1016/j.bj.2020.11.005.
[61] Michele C, Maria ARDG, Giovanni NR. SARS-CoV-2: recent reports on antiviral therapies based on Lopinavir/Ritonavir, Darunavir/Umifenovir, Hydroxychloroquine, remdesivir, Favipiravir and other drugs for the treatment of the new coronavirus. Curr Med Chem 2020;27(July (27)):4536–41.
[62] ''An in-silico analysis of ivermectin interaction with potential SARS-CoV-2 targets and host nuclear importin α.'' https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7643422/. [Accessed 24 April 2021].
[63] ''Ivermectin as a promising RNA-dependent RNA polymerase inhibitor and a therapeutic drug against SARS-CoV2: Evidence from in silico studies,'' Sep. 09, 2020. https://www.researchsquare.com. [Accessed 24 April 2021].
[64] Kandeel M, Al-Nazawi M. Virtual screening and repurposing of FDA approved drugs against COVID-19 main protease. Life Sci 2020;251 (June):117627. http://dx.doi.org/10.1016/j.lfs.2020.117627.
[65] Alexpandi R, De Mesquita JF, Pandian SK, Ravi AV. Quinolines-based SARS-CoV-2 3CLpro and RdRp inhibitors and Spike-RBD-ACE2 inhibitor for drug-repurposing against COVID-19: an in silico analysis. Front Microbiol 2020;11. http://dx.doi.org/10.3389/fmicb.2020.01796.
[66] Elmezayen AD, Al-Obaidi A, ahin AT, Yelekçi K. Drug repurposing for coronavirus (COVID-19): in silico screening of known drugs against coronavirus 3CL hydrolase and protease enzymes. J Biomol Struct Dyn 2021;39(May (8)):2980–92. http://dx.doi.org/10.1080/07391102.2020.1758791.
[67] Trezza A, Iovinelli D, Santucci A, Prischi F, Spiga O. An integrated drug repurposing strategy for the rapid identification of potential SARS-CoV-2 viral inhibitors. Sci Rep 2020;10(August (1)):13866. http://dx.doi.org/10.1038/s41598-020-70863-9.
[68] Jockusch S, Tao C, Li X, Chien M, Kumar S, Morozova I, et al. Sofosbuvir terminated RNA is more resistant to SARS-CoV-2 proofreader than RNA terminated by Remdesivir. Sci Rep 2020;10(1). http://dx.doi.org/10.1038/s41598-020-73641-9.
[69] Hall DC, Ji H-F. A search for medications to treat COVID-19 via in silico molecular docking models of the SARS-CoV-2 spike glycoprotein and 3CL protease. Travel Med Infect Dis 2020;35(June):101646. http://dx.doi.org/10.1016/j.tmaid.2020.101646.
[70] Elfiky AA. Ribavirin, remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): a molecular docking study. Life Sci 2020;253(July)117592. http://dx.doi.org/10.1016/j.lfs.2020.117592.
[71] Mittal L, Kumari A, Srivastava M, Singh M, Asthana S. Identification of potential molecules against COVID-19 main protease through structure-guided virtual screening approach. J Biomol Struct Dyn 2020;1–19(May). http://dx.doi.org/10.1080/07391102.2020.1768151.
[72] Musarrat F, et al. The anti-HIV drug nelfinavir mesylate (Viracept) is a potent inhibitor of cell fusion caused by the SARSCoV-2 spike (S) glycoprotein warranting further evaluation as an antiviral against COVID-19 infections. J Med Virol 2020;92(October (10)):2087–95. http://dx.doi.org/10.1002/jmv.25985.
[73] Ohashi H, et al. Multidrug treatment with nelfinavir and cepharanthine against COVID-19. bioRxiv)2020;(April). http://dx.doi.org/10.1101/2020.04.14.039925. 2020.04.14.039925.
[74] Altay O, et al. Current status of COVID-19 therapies and drug repositioning applications. iScience 2020;23(July (7)):101303. http://dx.doi.org/10.1016/j.isci.2020.101303.
[75] Keretsu S, Bhujbal SP, Cho SJ. Rational approach toward COVID-19 main protease inhibitors via molecular docking, molecular dynamics simulation and free energy calculation. Sci Rep 2020;10(October (1)):17716. http://dx.doi.org/10.1038/s41598-020-74468-0.
[76] Awad IE, Abu-Saleh AA-AA, Sharma S, Yadav A, Poirier RA. High-throughput virtual screening of drug databanks for potential inhibitors of SARS-CoV-2 spike glycoprotein. J Biomol Struct Dyn 2020;(October):1–14. http://dx.doi.org/10.1080/07391102.2020.1835721.
[77] Anwar MU, et al. Combined deep learning and molecular docking simulations approach identifies potentially effective FDA approved drugs for repurposing against SARS-CoV-2, preprint;May 2020. http://dx.doi.org/10.26434/chemrxiv.12227363.v1.
[78] Koulgi S, et al. Drug repurposing studies targeting SARS-CoV-2: an ensemble docking approach on drug target 3C-like protease (3CLpro). J Biomol Struct Dyn 2020;(July):1–21. http://dx.doi.org/10.1080/07391102.2020.1792344.
[79] Al-Tawfiq JA, Al-Homoud AH, Memish ZA. Remdesivir as a possible therapeutic option for the COVID-19. Travel Med Infect Dis 2020;34:101615. http://dx.doi.org/10.1016/j.tmaid.2020.101615.
[80] Deb P, Molla MdMA, Saif-Ur-Rahman KM. An update to monoclonal antibody as therapeutic option against COVID-19. Biosaf Health 2021;3 (2):87–91. http://dx.doi.org/10.1016/j.bsheal.2021.02.001.
[81] Jin P, Li J, Pan H, Wu Y, Zhu F. Immunological surrogate endpoints of COVID-2019 vaccines: the evidence we have versus the evidence we need. Signal Transduct Target Ther 2021;6(1):48. http://dx.doi.org/10.1038/s41392-021-00481-y.
[82] Kurtzberg J, et al. Allogeneic human mesenchymal stem cell therapy (Remestemcel-L, Prochymal) as a rescue agent for severe refractory acute

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graft-versus-host disease in pediatric patients. Biol Blood Marrow Transplant 2014;20(2):229–35. http://dx.doi.org/10.1016/j.bbmt.2013.11.001.

[83] Ben-Zvi I, Kivity S, Langevitz P, Shoenfeld Y. Hydroxychloroquine: from malaria to autoimmunity. Clin Rev Allergy Immunol 2012;42(2):145–53. http://dx.doi.org/10.1007/s12016-010-8243-x.

[84] Hwang S-W, Oh D-J, Lee D, Kim J-W, Park S-W. Clinical efficacy of 25% l-ascorbic acid (C'ensil) in the treatment of melasma. J Cutan Med Surg 2009;13(March (2)):74–81. http://dx.doi.org/10.2310/7750.2008.07092.

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