Antiviral drugs prioritization for COVID-19 management based on rational selection

Rakesh S. Joshi[1,2,*], Ashok P. Giri[1,2], Mahesh J. Kulkarni[1,2], Mahesh Gupta[3], Savita Verma[3], Dhruva Chaudhry[3], Narendra Deshmukh[4] and Anita Chugh[4,*]

[1]Biochemical Sciences Division, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India
[2]Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201 002, India
[3]Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak 124 001, India
[4]INTOX Private Limited, Pune 412 115, India

The SARS-CoV-2 infection has resulted in COVID-19 pandemic worldwide. It has infected around 0.1 billion individuals and caused 2 million fatalities across the globe till mid-January 2021. Drug repurposing has been utilized as the most preferred therapeutic intervention for COVID-19 mitigation due to its necessity and feasibility. To prioritize therapeutic regime against COVID-19, we used 61 antiviral drugs and their combinations. Selected molecules were subjected to virtual screening against: (i) human angiotensin-converting enzyme 2 receptor binding domain (hACE-2) which serves as an anchor for virus attachment and entry, (ii) SARS-CoV-2 RNA dependent RNA polymerase (RdRp) responsible for viral RNA replication, and (iii) SARS-CoV-2 main protease (M^{Pro}) needed for viral polyprotein slab proteolytic processing. Based on docking score, pharmacodynamic and pharmacokinetic parameters, combinations of Daclatasvir, Elbasvir, Indinavir, Ledipasvir, Paritaprevir and Rilpivirine were analysed further. Our analysis suggested Sofosbuvir in combination with Ledipasvir and Daclatasvir as potential therapeutic agents for SARS-CoV-2. The combined score suggests that these combinations have superior anti-SARS-CoV-2 potential than Remdesivir and other investigational drugs. The present work provides a rationale-based approach to select drugs with possible anti-SARS-CoV-2 activity for further clinical evaluation.

Keywords: Drug repurposing, hACE-2, main protease, RNA dependent RNA polymerase, SARS-CoV-2.

GLOBAL spread and infection of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) resulted in COVID-19 pandemic. More than 0.1 billion have been infected with a mortality rate up to 5% till the end of January 2021 (ref. 1). Due to the unavailability of a specific therapeutic regime, COVID-19 management is challenging. Drug repurposing offers a speedy solution for COVID-19 mitigation. Ongoing application of repurposed drugs aims to control symptoms of the disease or attain antiviral effect (viral replication cycle). Danoprevir, Darunavir, Favipiravir, Lopinavir/Ritonavir, Oseltamavir, Remdesivir and Umifenovir have been tested clinically against SARS-CoV-2 (ref. 2).

Furthermore, non-antiviral drugs like Camostat or Nafamostat, Chloroquine, Hydroxychloroquine, and Ivermectin have shown anti-SARS-CoV-2 potential[3]. Literature suggests that targeting multiple closely interacting pathogenesis-related proteins can provide effective intervention. Hence, several treatments and clinical trials used combinations of antiviral drugs for viral infection management. We selected three targets from the interaction network of pathogenesis. These targets are the virus entry point, Human angiotensin-converting enzyme 2 receptor binding domain (hACE-2), SARS-CoV-2 RNA dependent RNA polymerase (RdRp) for viral RNA replication and SARS-CoV-2 main protease (M^{Pro}) for virus maturation[4].

SARS-CoV-2 attaches and infects human cells through hACE-2 receptor[5,6]. The extracellular domain of hACE-2 serves as SARS-CoV-2 spike (S) receptor. Cleavage product of S protein, S1, interacts with hACE-2 and anchors to the viral membrane by S2 protein[6–8]. SARS-CoV-2 shows strong binding (~10 fold) with hACE-2 compared to other coronaviruses, hence, serving as a vital target for intervention[5]. Multiprotein complex facilitates the replication of SARS-CoV-2 RNA genome and serves as a therapeutic target. RNA-dependent RNA polymerase (RdRp or NSP12), a cleavage product of viral polyproteins (ORF1a and ORF1b), catalyses the replication and transcription cycle of the virus. Due to its essentiality, RdRp has been explored as one of the primary targets for nucleoside analogues antivirals, e.g. Remdesivir[9,10]. Self-maturation and processing of viral replicase enzymes can be targeted by inhibition of papain-like main protease (M^{Pro})[11,12]. Due to low similarity with human proteases, inhibitors of M^{Pro} show minimal cross-reactivity[11,13].

Molecules inhibiting viral entry, replication and maturation can have the potential anti-SARS-CoV-2 activity. Sixty one approved antiviral drugs were screened *in silico* for binding against selected targets. A combined activity

*For correspondence. (e-mail: rs.joshi@ncl.res.in; anita.chugh@intoxlab.com)

score was calculated based on differential binding energy to targets. Further, pharmacokinetic and pharmacodynamic parameters were calculated to prioritize drug candidates for repurposing for COVID-19 management.

Methods

Library and target molecules preparation

Approved antivirals library was generated using three-dimensional structures from PubChem[14]. They were checked for stereochemical properties, followed by conversion to *.pdbqt format by Autodock Tools[15]. The library was used for further docking studies. The necessary methodology was as described by an earlier study[4].

Experimental structures of hACE-2 complexed with viral spike protein (PDB ID: 6VW1) and M^{Pro} (PDB ID: 6Y2F) were downloaded from PDB[7,11]. After the receptor preparation process on M^{Pro}, the grid for docking simulation was set using AutoGrid program around active site residues H41 and C145 with 36 × 56 × 40 Å dimension[15] and structure converted to *.pdbqt format. Similarly, the structure of SARS-CoV-2 RdRp (PDB: 7BTF) was prepared by generating a grid of 34 × 34 × 36 Å dimension around RNA binding pocket[9]. Furthermore, the grid for hACE2 was 20 × 38 × 24 Å spanning the viral spike protein recognition residues (K31, E35, D38, M82, K353)[7]. These target molecules were then further used for virtual screening.

Virtual screening using combined score analysis

The prepared receptor molecules from custom-made libraries were set for virtual screening by AutoDock Vina using default parameters[16]. Top hits of ligands were selected based on their docking scores. Comparative analysis of binding score and the combined score was performed using heatmap analysis, followed with hierarchical clustering and rank product analysis. Relative weightage was assigned as follows: M^{Pro} = 20%; RdRp = 20% and hACE-2 = 60%. The combined activity score was calculated as ((binding energy M^{Pro} *0.2) + (binding energy RdRp *0.2) + (binding energy hACE-2*0.6)). Ligands with high solubility and bioavailability were further taken for interaction analysis. A detailed methodology of interaction analysis was as described by an earlier study[4].

Results and discussion

Outcomes of *in silico* screening of antiviral drugs demonstrate several molecules' potential to intervene SARS-CoV-2 infection cycle. They can potentially offer avenues to manage COVID-19. Remdesivir, Lopinavir/Ritonavir (Kaletra)[17,18], Favipiravir[19] and Umifenovir are among top antivirals being focused on for COVID-19 management. Nucleotide analogue, Remdesivir, serve as broad-spectrum antiviral against RNA viruses like Coronaviridae. Initial preclinical and clinical studies indicated Remdesivir causing a reduction in viral load through RdRp inhibition[10]. Remdesivir exhibited binding energy –7.8, –8.2 and –7.2 kcal/mol against hACE-2, M^{Pro} and RdRp respectively (Figure 1). Remdesivir has a higher

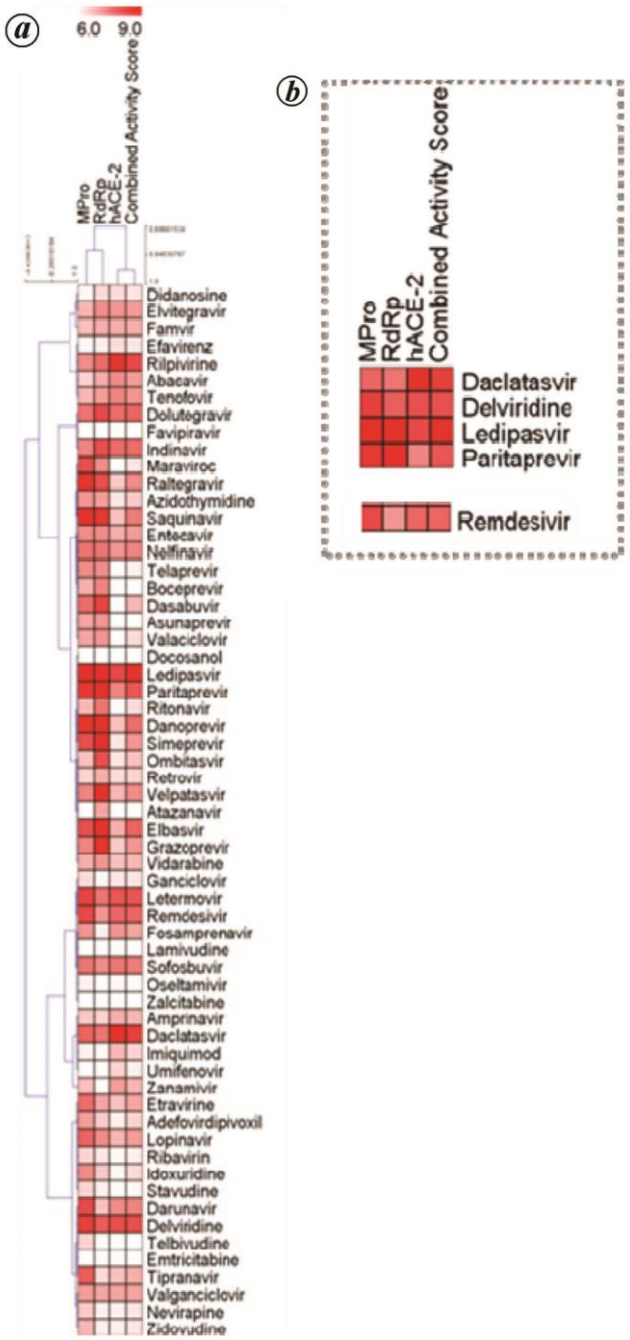

Figure 1. ***a***, Heatmap with hierarchial clustering for binding and combined score analysis of screened antivirals. ***b***, Ranking of binding score indicating top molecules.

Table 1. Drug candidates exhibiting strong binding to M^{Pro}/RdRp/hACE-2

Target	Binding energy range* (kcal/mol)	Drug	Binding energy (kcal/mol)	Combined activity score
M^{Pro}	–3.2 to –10.2	Remdesivir	–8.2	7.8
		Ledipasvir	–9.4	8.8
		Saquinavir	–9.0	7.5
		Danoprevir	–8.7	7.7
		Raltegravir	–8.7	7.3
RdRp	–3.2 to –9.4	Remdesivir	–7.2	7.8
		Ledipasvir	–10.2	8.8
		Elbasvir	–10.0	7.8
		Danoprevir	–9.8	7.7
		Paritaprevir	–9.4	8.0
hACE-2	–2.8 to –8.9	Remdesivir	–7.8	7.8
		Daclatasvir	–8.9	8.4
		Rilpivirine	–8.7	8.2
		Ledipasvir	–8.2	8.8

Drugs exhibiting low binding energy to either M^{Pro}/RdRp/hACE-2 are shortlisted. *Range of 61 antiviral drugs screened.

Table 2. Binding energy and combined activity scores for approved antiviral drugs exhibiting hACE-2 binding better than or comparable to Remdesivir

Drug	Binding energy (kcal/mol) M^{Pro}	RdRp	hACE-2	Combined activity score
Combined activity score significantly better than Remdesivir				
Ledipasvir	–9.4	–10.2	–8.2	8.8
Daclatasvir	–7.8	–7.6	–8.9	8.4
Combined activity score comparable to Remdesivir				
Rilpivirine	–7.3	–7.7	–8.7	8.2
Delviridine	–8.4	–7.9	–8.1	8.1
Paritaprevir	–8.6	–9.4	–7.4	8.0
Letermovir	–8.3	–7.6	–8.0	8.0
Dolutegravir	–7.6	–8.2	–7.7	7.8
Remdesivir*	–8.2	–7.2	–7.8	7.8*
Indinavir	–7.4	–8.1	–7.7	7.7
Sofosbuvir*	–7.6	–7.3	–7.6	7.5
Darunavir	–8.2	–6.7	–7.3	7.4
Abacavir*	–6.5	–6.9	–7.3	7.4*
Tenofovir*	–6.8	–7.1	–7.4	7.1*

*These drugs are converted intracellularly to active metabolites. The binding energy of known key active metabolite present intracellularly was considered for M^{Pro} and RdRp for combined activity score determination.

combined activity score compared to selected repurposed antiviral and non-antiviral drugs against SARS-CoV-2. Selected drugs and their metabolites binding energy and combined activity are provided in Supplementary Table 1.

Binding energy and combined activity score for selected antiviral drugs are shown in Supplementary Table 2. The binding energy of approved antiviral drugs for respective target is outlined in Table 1.

Ledipasvir, Elbasvir, Danoprevir, Saquinavir and Paritaprevir showed strong binding with (<–9 kcal/mol) either target. Candidates having lower binding energy against hACE-2 than Remdesivir were shortlisted for further evaluation (Table 2).

Daclatasvir and Ledipasvir depicted better combined activity score than Remdesivir (>8.2) and strong hACE-2 binding (≤ –8.2 kcal/mol). Daclatasvir and Ledipasvir are used as combination therapy against Hepatitis C Virus (HCV) infection[20–22]. They inhibit HCV RNA replication and assembly of virions by blocking non-structural Protein 5A (NS5A). They are FDA approved against HCV infections as the fixed-dose combination (FDC) with Sofosbuvir[22,23].

From *in silico* analysis, Ledipasvir was found to be a top hit for drug repurposing. For M^{Pro} and RdRp, it has a binding energy of < –9 kcal/mol and against hACE-2 ≃8.2 kcal/mol. Amongst the screened antivirals, Daclatasvir binds strongly with hACE-2 and interfere with its binding to spike protein of SARS-CoV-2. Daclatasvir interaction with the binding pocket of targets is shown in Figure 2, and pharmacokinetic overview of these drugs is summarized in Table 3.

Remdesivir (GS-5734) is used as a reference molecule in the current study. It is prodrug form of adenosine analogue (GS-441524) and can be intracellularly metabolized to an active nucleoside triphosphate (NTP)[10]. Pro- and metabolite forms of Remdesivir exhibit strong binding against RdRp and M^{Pro} (Supplementary Table 1). The prodrug can bind to hACE-2 weakly for a prolonged time due to its extended half-life, while, the parent molecule, Remdesivir, has effective hACE-2 inhibition for a shorter duration due to short half-life (Table 3).

The half-life for Ledipasvir and Daclatasvir is 47 h and 12 to 15 h respectively. Due to longer half-life, they can have a long-term binding with hACE-2. Additionally, due to significant intracellular concentrations, they show noteworthy binding against RdRp and M^{Pro}. Hence,

Table 3. Pharmacokinetic properties of lead candidates and reference drug (Remdesivir*)

	Remdesivir*	Ledipasvir	Daclatasvir
Status	Investigational	Approved	Approved
Indication (*in clinics)	SARS-COV-2	Chronic HCV genotype 1a, 1b, 4, 5 and 6 infection in combination with Sofosbuvir (Harvoni)	Chronic HCV genotype 1, 3 and 4 infection in combination with Sofosbuvir, Ribavirin or interferon
The key known target for the approved indication	RdRp inhibition by triphosphate metabolite (NTP)	Prevent hyperphosphorylation of NS5A	Prevent hyperphosphorylation of NS5A
Bio-availability	Not available	76%	67%
Protein binding	Not available	>99.8%	99%
Elimination half-life	0.4 h parent (non-human primate (NHP)) 20 h for NTP metabolite in humans, 14 h in NHP	47 h (median terminal)	12–15 h
Metabolism	Not available	No detectable metabolism excretion–unchanged in faeces	Faecal (53% as unchanged drug), kidney

Daclatasvir and Ledipasvir are considered for repurposing against COVID-19.

Route of administration for Remdesivir is intravenous, whereas Daclatasvir and Ledipasvir, are orally administered. Combinations of Ledipasvir and Daclatasvir with Sofosbuvir are clinically approved. In docking analysis, Sofosbuvir also exhibited high combined activity score of 7.5. Thus, the additive putative synergistic effect could be expected in these approved antiviral drug combinations and they provide merit over other drugs' combinations for COVID-19 management. Due to moderate to better protein binding capacity of these molecules, high drug concentration becomes available to bind against the extracellular hACE-2 target. Furthermore, the circulating half-life of Sofosbuvir is 0.4 h. It is metabolized as triphosphate form GS-46103 (2′-deoxy-2′-α-fluoro-β-C-methyluridine-5′-triphosphate) and dephosphorylated metabolite GS 331007 subsequently, which has an elimination half-life of 27 h. Thus, Sofosbuvir can bind for a longer time to intracellular targets such as RdRp and M^{Pro} (Supplementary Table 3).

In the case of approved Daclatasvir and Sofosbuvir combination with Ribavarin for HCV treatment, Ribavarin did not exhibit good combined activity score (6.2) against SARS-CoV-2 targets. Hence, Ribavarin was not considered for prioritization (Supplementary Table 2)[23]. Similarly, another fixed-dose combination (FDC) of Daclatasvir with Asunaprevir against HCV showed low combined activity score (5.7) for Asunaprevir. Hence Asunaprevir was dropped from further analysis.

Combined scores for Rilpivirine, Viridine, Paritaprevir, Letermovir and Dolutegravir are better than Remdesivir (7.8 to 8.3)[24]. Rilpivirine binds strongly to hACE-2 and Paritaprevir showed higher binding to RdRp and M^{Pro}. All these drugs can bind to hACE-2 in pro-form and have high protein binding (Supplementary Table 4). Non-nucleoside reverse transcriptase inhibitors (NNRTI) like Rilpivirine and Delviridine are approved against HIV-1 infections[25–27]. As a second-line therapy drug Delaviridine is inconvenient due to its dosing schedule, it is therefore dropped from further evaluation.

Paritaprevir in combination with Ombitasvir, Dasabuvir, Ritonavir, and Ribavirin is used to treat HCV[28]. Most of these antivirals exhibited low binding score against all targets and thus have negligible anti-SARS-CoV-2 potential.

Abacavir, Darunavir, Indinavir, Sofosbuvir and Tenofovir showed high binding to SARS-CoV-2 target. Short half-life, moderate protein binding (60%), acceptable safety profile and strong hACE-2 binding (–7.7 kcal/mol) makes Indinavir a potential agent. Indinavir and Ritonavir FDC is used for HIV treatment. Ritonavir has a low combined activity score, but it blocks the intracellular conversion of Indinavir and thus prolongs its half-life. Hence, the FDC of Indinavir and Ritonavir can be anti-SARS-CoV-2 (ref. 29). The development of new FDC of these drugs for intravenous use can be considered in critically ill patients (Supplementary Table 1).

Short half-life (1.54 ± 0.63 h) and moderate protein binding (50%), with a binding energy of –7.3 kcal/mol against hACE-2 suggest the potential of Abacavir for effective intervention. Abacavir and its metabolite Carbovir triphosphate depicted high binding energy against M^{Pro} and RdRp (Supplementary Table 3)[30]. In HIV infection, Abacavir combination with Lamivudine, Zidovudine and Dolutegravir is used for the treatment. The Lamivudine and Zidovudine have combined activity scores 5.3 and 6.3 respectively. Due to good combined activity score, high protein binding and half-life of 14 h, Dolutegravir and Abacavir combination are preferred over a combination with Lamivudine or Zidovudine for COVID-19. Elbasvir has the potential against SARS-CoV-2 replication and maturation due to high binding to RdRp (–10 kcal/mol) and combined activity score of 7.8. This

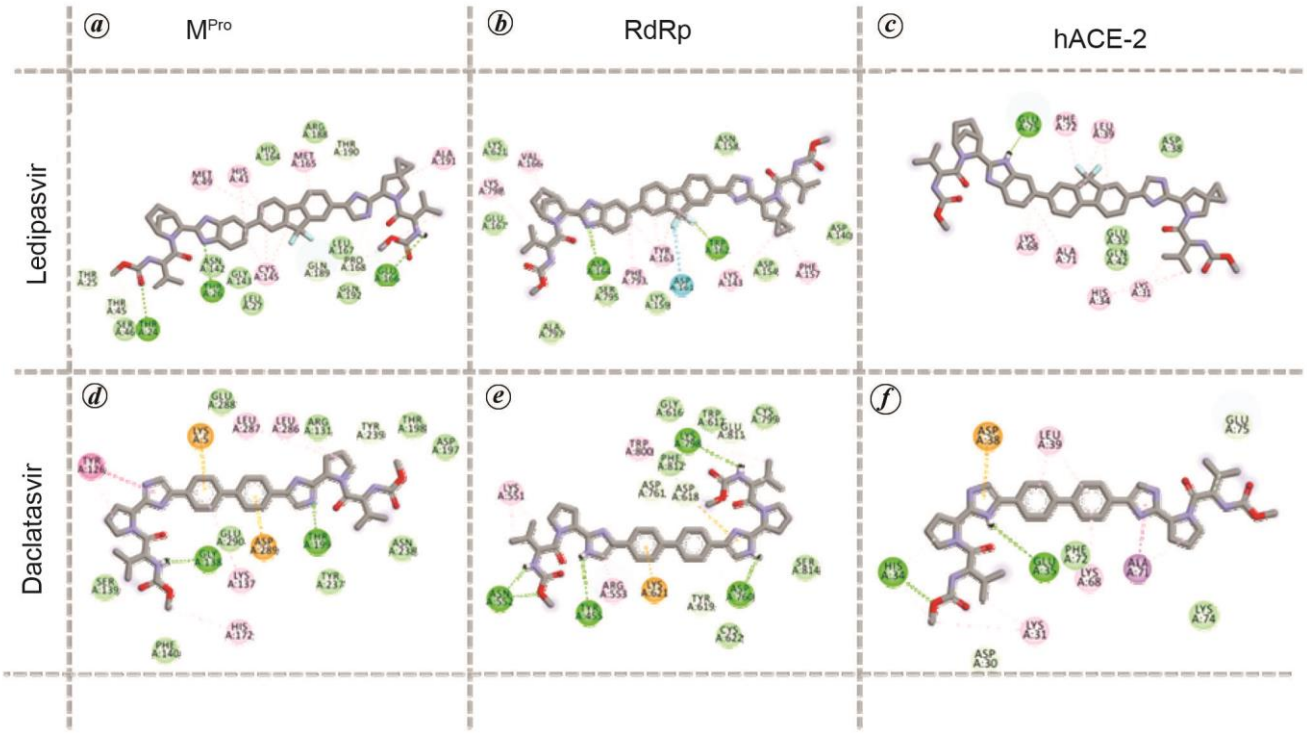

Figure 2. Molecular interaction of Ledipasvir with binding pocket of (***a***) M^{Pro}, (***b***) RdRp and (***c***) hACE-2. Likewise, Daclatasvir also showed stronger binding and multiple interactions with binding sites of (***d***) MPro, (***e***) RdRp and (***f***) hACE-2.

drug has a half-life (geometric mean) of 24 h and can be evaluated as a candidate drug for COVID-19. Elbasvir is a direct-acting antiviral which inhibits HCV NS5A protein and approved as the FDC with Grazoprevir or Ribavarin and is a part of combination therapy to treat HCV[22,31]. Grazoprevir exhibits a combined activity score of 7.2 and shows low binding energy for RdRp (–8.7 kcal/mol), superior to Ribavarin. Hence, FDC of Elbasvir with Grazoprevir can be checked for COVID-19 management.

Danoprevir, NS3/4A protease inhibitor approved for HCV, exhibits distinctly better binding for M^{Pro} (–8.7 kcal/mol) and RdRp (–9.8 kcal/mol). Danoprevir half-life and protein binding information are not available in the public domain; also, it showed poor binding to hACE-2. It does not offer an advantage over other lead candidates. Another protease inhibitor, Saquinavir, exhibits high binding to M^{Pro} (–9.0 kcal/mol). Due to its low combined activity score (7.5) and poor bioavailability, it is not considered for prioritization. Earlier *in silico* studies have identified two non-antiviral drugs Ergotamine and Ubrogepant as potential anti-SARS-CoV-2 agents (Supplementary Table 5)[32,33]. These molecules exhibited the potential to bind to all three targets. Binding energy at the crucial target of interest hACE-2 for Ubrogepant was –7.0 kcal/mol. Ergotamine showed strong binding against all three targets as compared to Ledipasvir (Supplementary Table 5), while Daclatasvir showed stronger hACE-2 binding compared to Ergotamine[32]. It has been observed that cardiovascular drugs like ACE inhibitors and angiotensin receptor antagonists do not show affinity toward hACE-2 (ref. 34). Hence, this further strengthens the case for Daclatasvir and Ledipasvir's prioritization as lead candidates for COVID-19 over Ergotamine and other similar drugs.

Cleavage of S2 protein is catalysed by a human cell surface serine protease, TMPRSS2[6,35]. Therefore, along with hACE-2, TMPRSS2 can be considered for effective targeting of viral replication and maturation. Camostat and Nafamostat have demonstrated inhibition of TMPRSS2[5,36]. Hence, Camostat and Nafamostat and their combinations with antiviral drugs with high binding for hACE-2 such as Daclatasvir and Rilpivirine can offer synergistic effects against SARS-CoV-2.

We suggest that molecules with potential for strong hACE-2 binding with RdRp and M^{Pro} interaction can be repurposed against SARS-CoV-2. Additionally, due to better protein binding and long half-life, suggested drug/drug combinations can exhibit activity better than other drugs under investigation. Further, shortlisted drugs are orally administered and thus offer an advantage over others. There is a need for systematic preclinical and clinical assessment for these drugs and their FDC for anti-SARS-CoV-2 activity. These repurposed drugs might provide potential antiviral effect against SARS-CoV-2 better than other drugs under trials and tested investigational drugs.

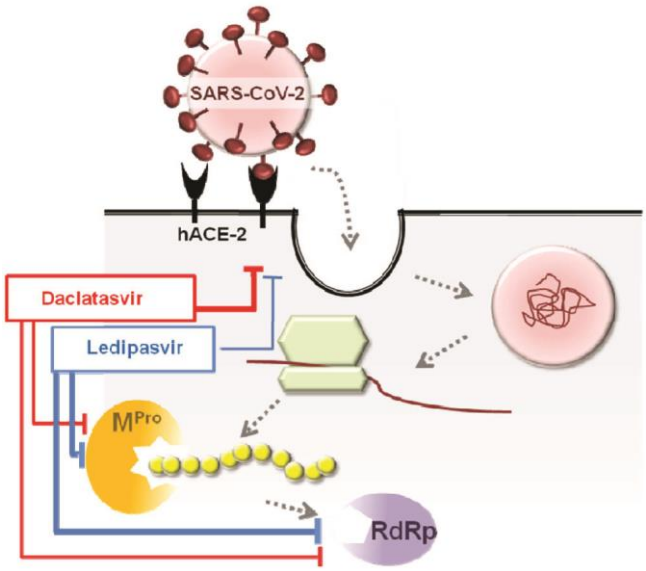

Figure 3. Schematic representation of predicted actions of Ledipasvir and Daclatasvir against multiple targets in SARS-CoV-2. Ledipasvir prominently targeting M^{Pro} and RdRp is indicated by the thick blue lines and binding moderately to hACE-2 is illustrated by relatively thin blue line. In the case of Daclatasvir, binding is strong with hACE-2 and is indicated by a thick red line. Daclatasvir binds moderately to M^{Pro} and RdRp which is indicated by thin red lines.

Conclusion

We virtually identified drugs with potential to bind to multiple targets like SARS-CoV-2 M^{Pro} and RdRp; and hACE-2 (Figure 3). These repurposed drugs are likely to have anti-SARS-CoV-2 activity by impacting virus entry, replication and maturation.

Daclatasvir, Elbasvir, Indinavir, Ledipasvir, Paritaprevir and Rilpivirine were predicted as potential anti-SARS-CoV-2 based on combined activity score, pharmacokinetic and pharmacodynamic parameters. Ledipasvir and Daclatasvir emerged as lead candidates with high combined activity scores and prolonged half-life, ensuring significant extracellular hACE-2 engagement along with RdRp and M^{Pro}. With good safety profile and oral administration of Ledipasvir, Daclatasvir and other drugs selected through this screening, can provide an advantage over others. These drugs and their FDCs can be considered for systematic fast track preclinical and clinical evaluation for COVID-19 management. Our findings provide a scientific rationale for applying Ledipasvir and Daclatasvir in combination with Sofosbuvir for COVID-19 management. Recent initial clinical trials data from Iran with Ledipasvir and Daclatasvir in combination with Sofosbuvir against COVID-19 are encouraging. Based on our analysis and available preclinical and clinical data, we recommend prioritization and aggressive perusal of clinical evaluation of these drug combinations.

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