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Union is strength: antiviral and anti-inflammatory drugs for COVID-19

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Several clinical trials to treat Coronavirus 2019 (COVID-19) are in progress around the world. Some of them rely on clinical experience, whereas others include computational predictions. Here, we provide an overview of current efforts in the search for COVID-19 therapies, focusing on structural information of relevant targets. We elaborate on a robust pharmacological rationale for the repurposing of existing drugs, highlighting key advantages of dual therapies with antiviral and anti-inflammatory activity. Furthermore, we provide a consensus list of molecules that could undergo preliminary randomized clinical trials against COVID-19.

Introduction

The COVID-19 outbreak has quickly reached pandemic dimensions because of fast human-to-human transmission. The first reports of the disease date from December 2019 in Wuhan, China. The causal agent of this disease is a novel beta-coronavirus of unclear origin called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1]. According to Johns Hopkins University, as of October 2020 is > 44, 400, 000 people have been infected, and >1,173,000 have died. The mortality rate of this disease has been estimated at 3.6–5.7% [2], and its transmission rate is high compared with other coronaviruses, with a basic reproductive number of 2–3 [3]. COVID-19 shows a range of clinical manifestations, such as fever, cough, dyspnea, pneumonia, acute respiratory distress syndrome, and shock [4]. Furthermore, data suggest that asymptomatic carriers can also spread the disease [5]. Even more worrisome is that it has not been demonstrated that patients who recover from COVID-19 acquire long-term immunity, and there is no evidence that re-infection is not possible even in immunocompetent individuals [6]. Thus, the rapid development of effective treatments to control this disease is a worldwide priority.

Several prophylactic and therapeutic schemes are in progress, and others are under development, such as pharmacological agents, vaccines, and serum from recovered patients [7,8]. Nevertheless, standard therapies are not yet available. The National Institutes of Health (NIH) recommend treatment guidelines to inform clinicians on how to care for patients with COVID-19. The NIH clinical guidelines (https://www.covid19treatmentguidelines.nih.gov/) currently recommend only remdesivir and corticosteroids as useful pharmacological therapies against COVID-19. For other patients, best supportive care is the only recommendation [9]. These guidelines are continuously updated as understanding of COVID-19 increases.

Over the past few months, a large volume of information regarding the biology and pathogenesis of SARS-CoV-2 has been

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generated. The proper use of this information is valuable for the development of new therapies, particularly if it is analyzed from different perspectives including computer-based methodologies, as well as biological, chemical, and pharmacological knowledge. Here, we review the biology of SARS-CoV-2, focusing on pharmacologically relevant targets. We also provide a detailed discussion of the structural information of relevant targets of SARS-CoV-2. We then present a virtual screening (vs) scheme for the repurposing of current drugs against COVID-19 in the context of the massive amount of information available. We provide medical considerations for the repurposing of drugs, focusing on patients moderately ill with COVID-19, and propose drug products, including those under development, that are available and accessible in many countries.

SARS-CoV-2 biology and pathogenesis

Coronaviruses are enveloped positive-sense single-stranded RNA viruses. SARS-CoV-2 is a beta-coronavirus, similar to SARS-CoV and Middle East Respiratory Syndrome (MERS)-CoV, with which it shares ~79% and 50% of its genome, respectively [10]. Furthermore, SARS-CoV-2 shares up to 96% of its genome with bat coronaviruses [11]. RNA viruses are well known for having high mutation rates [12]; however, coronaviruses display a lower mutation rate than expected because they express a proofreading exonuclease [13]. For SARS-CoV-2, two different strains have been identified that have different clinical significance [14]. It has been suggested that point mutations, such as D614 G, could render the virus more infectious [15]. The envelope of SARS-CoV-2 comprises a phospholipid bilayer with inserted proteins, namely: the spike protein, hemagglutinin-esterase, envelope, and membrane proteins [16]. The spike protein on the envelope of SARS-CoV-2 interacts with angiotensin-converting enzyme 2 (ACE2) to infect the host [17]. Notably, SARS-CoV-2 binds to ACE2 with higher affinity than do other beta-coronaviruses [16] and it has a furin cleavage site that is not present in other viruses of the same clade [18].

The virion nucleocapsid occurs inside the double-layered phospholipid envelope. Studies on other coronaviruses, such as SARS-CoV, show that, once the virion gets into the cell and the nucleocapsid reaches the cytoplasm, the single-strand RNA translates into a replicase polyprotein [including proteases, helicases, RNA-dependent RNA polymerase (RdRp), and several other proteins]. Then, multiple subgenomic RNA sequences are generated through negative-strand intermediates, using the viral genome as a template. After translation, the future envelope proteins are inserted into the endoplasmic reticulum–Golgi intermediate compartment (ERGIC), and the nucleocapsid also invaginates into this compartment. Finally, new virions are exported from the cell through ERGIC vesicles [19].

Notably, the inflammatory response triggered by the virus appears to be leading to higher morbimortality of SARS-CoV-2 compared with SARS-CoV. In some cases, the inflammatory response progresses to acute respiratory distress syndrome and disseminated intravascular coagulation [16,20]. Angioedema at the respiratory level might be mediated by several inflammatory cytokines, including bradykinin, and its progression leads to viral sepsis and multiorgan failure [21]. To avoid this complex scenario, early pharmacological strategies must be developed. Acknowledging that monotherapy might not be enough, dual therapies must be sought.

Molecular description and analysis of relevant anti-COVID-19 targets

Several steps in the viral replication cycle could be disrupted pharmacologically (see [7] for a comprehensive review). As of October 2020, the efforts to elucidate the main macromolecular machinery of the SARS-CoV-2 virus have resulted in 330 crystallographic structures deposited in the Protein Data Bank (www.rcsb.org) of >25 different forms SARS-CoV-2 proteins either in their apo or holo conformations or in complex with different ligands. The most studied druggable targets for COVID19 are the main protease, the spike protein, RdRp, and the papain-like protease, among others. As depicted in Fig. 1, the most studied druggable targets for COVID19 are the main protease, the spike protein, RdRp, and the papain-like protease, among others. In addition, inhibiting human targets, such as furin or TMPRSS2, could be useful in fighting SARS-CoV-2 infection.

Main protease

The main protease (M^{pro}) is a nonstructural protein (nsp5) that assists in viral replication by processing precursors of coronavirus structural proteins that are translated together [22]. Thus, inhibiting M^{pro} might lead to attenuation of the viral infection. In addition, directly inhibiting the catalytic binding site, targeting dimerization sites is therapeutically attractive, because dimerization is required for the catalytic activity of this enzyme [23].

Several X-ray structures of SARS-Cov-2 M^{pro} have been published, with and without inhibitors [24,25]. The overall structure comprises three domains: the substrate-binding cleft is located between domains I and II; the catalytic site consists of well-defined subsites (S2′-S1′-S1-S2, S3, etc.) and the general recognition sequence is Leu-Gln↓(Ser, Ala, Gly) where ↓ indicates the cleavage site [24]; finally, domain III is involved in the dimerization of M^{pro} through a salt-bridge between the two protomers, thus framing the S1 subsite. The catalytic cysteine (Cys145) interacts with the inhibitor through functional groups, such as amides, aldehydes, or Michael acceptors. Along with Gly143, Cys145 and partly Ser144 form the canonical 'oxyanion hole'. Given that the sulfhydryl group is nucleophilic and easily oxidized, Zhang *et al*. [24] designed an inhibitor of the substrate-binding cleft. After considering absorption, distribution, metabolism, excretion, and toxicity (ADMET), physicochemical properties, and binding into M^{pro}, they found the optimal P groups to be P1 = γ-lactam; P2 = cyclopropyl; and P3 = pyridinone.

A summary of the main interactions observed for co-crystalized ligands in the catalytic binding site of M^{pro} is provided in Fig. 2. The height of the bars in Fig. 2a represents the frequency of a given interaction between M^{pro} and the ligands. Note that a given amino acid can have more than one interaction with the protein, such as hydrogen bonds, ionic interactions, and surface contacts. Most of the co-crystallized ligands interact with M^{pro} through Glu166, representing 92.3% of the molecules. Other common interactions include His164, Gly143, Cys145, and His163. All the co-crystallized ligands with M^{pro} resemble a similar molecular 'H' shape in the interaction pocket (Fig. 2b).

Lopinavir-ritonavir, putative M^{pro} inhibitors, failed to demonstrate efficacy in a recent clinical trial [26]. Interestingly, compu-

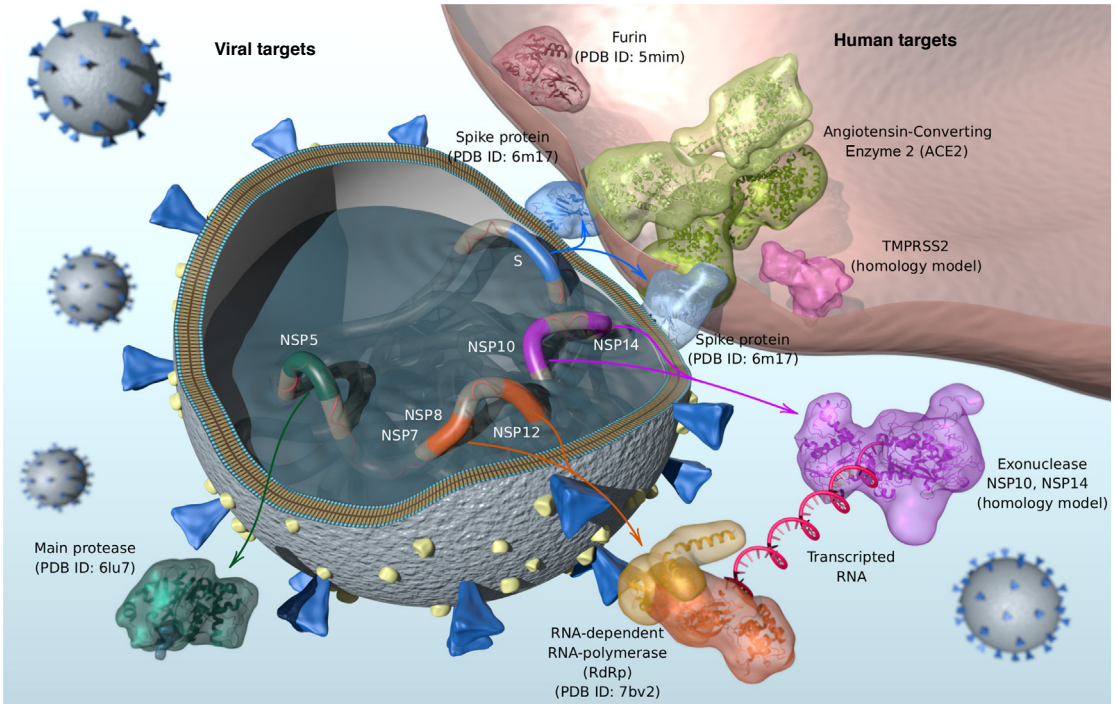

FIG. 1

General overview of potentially therapeutic viral and human targets involved in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. The viral capsid contains a single-stranded RNA genome that encodes different structural proteins, such as the spike protein [blue ribbons and surfaces; Protein Data Bank (PDB) ID 6m17]; and nonstructural proteins (nsp), including the main protease (green ribbons and surface; PDB ID 6lu7) and the mega-complex formed by the RNA-dependent RNA-polymerase (Rdrp; orange ribbons and surface; PDB ID 7bv2) with its co-factors NSP7 and NSP8 (yellow ribbons and surface) and the exonuclease formed by NSP10 and NSP14 (magenta ribbons and surface, model created by homology modeling). Some of the host targets relevant in SARS-CoV-2 infection are the furin protease (light-red ribbons and surface, PDB ID 5mim), the transmembrane protease TMPRSS2 (pink membrane, model created by homology modeling), and angiotensin-converting enzyme 2 (ACE2; light-green ribbons and surface, PDB ID 6m17), which binds to the viral spike protein.

tational and *in vitro* experimental data did not show inhibition of SARS-CoV-2 M^{pro} by these drugs [27,28]. Hence, the unpromising clinical results of lopinavir-ritonavir do not invalidate M^{pro} as a potential target for this disease.

RdRp

A set of nsps are responsible for the replication and transcription of SARS-CoV-2. RdRp (also known as nsp12) catalyzes the synthesis of viral RNA. It is proposed that RdRp requires the assistance of nsp7 and nsp8 as cofactors [29].

RdRp is considered a primary target for nucleotide-like inhibitors. Early docking studies with homology modeling suggested remdesivir as a good candidate against RdRp [30]. It is now clear from *in vitro* studies that remdesivir is an effective SARS-CoV-2 RdRp inhibitor [31,32]. Although clinical evaluation of remdesivir usefulness is ongoing, it has already shown promising results, such as reducing the time to recovery of symptoms from 15 days to 11 days (a reduction of almost 30%) [33,34]. Thereby, remdesivir received US Food and Drug Administration (FDA) approval for use in patients with severe COVID-19 [9]. The administration of favipiravir, another nucleotide analog prodrug, reduced the time to viral clearance to 4 days [35], and it has been granted clinical approval in Russia [36]. Therefore, RdRp is the first SARS-CoV-2 target to receive clinical approval. A recent *in silico* study suggested the antiviral drug sofosbuvir as a possible ligand to the SARS-CoV-2 RdRp active site; nevertheless, experimental validation is yet to be performed [37].

The crystallographic structure of SARS-CoV-2 RdRp was recently published in complex with nsp7 and nsp8 (PDB ID: 6M71; resolution of 2.9 Å). Also, sequence alignment showed that, along with the conserved architecture of the polymerase core of the viral polymerase family (RMSD of 0.82 with SARS-CoV RdRp), it has a beta-hairpin domain at its N terminus. The polymerase domain comprises three subdomains: a fingers subdomain (residues L366–A581 and K621–G679), a palm subdomain (residues T582–P620 and T680–Q815), and a thumb subdomain (residues H816–E920) [29].

The active site of the SARS-CoV-2 RdRp is in the palm domain, which includes seven polymerase motifs. Motif A contains a conserved divalent-cation-binding residue D618. Two zinc and three magnesium ions bound to metal-binding motifs were observed only in a second crystallography study containing the primer-template RNA and remdesivir triphosphate (PDB ID: 7BV2) [38]. Motif C (residues 753–767) contains the catalytic residues (759–SDD–761) in the turn between two β-strands. These catalytic residues are also conserved in most viral RdRps (e.g., 317–GDD–319 in hepatitis C virus ns5b and 327–GDD–329 PV 3Dpol), with the first residue being either serine or glycine.

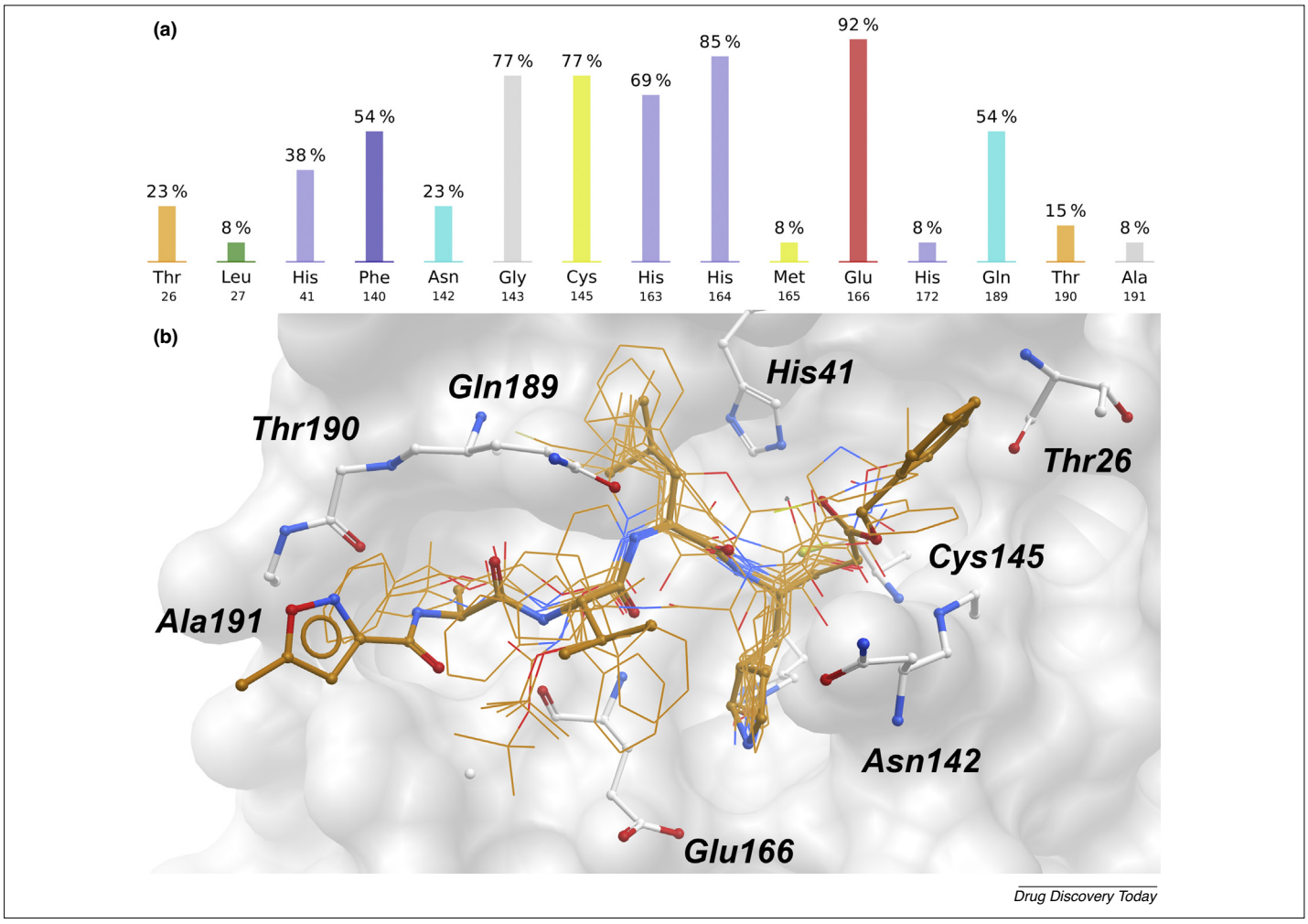

FIG. 2

Common interactions in ligands co-crystallized with M^{pro}. **(a)** Protein–ligand interaction fingerprint (PLIF) for ligands K36 [Protein Data Bank (PDB) ID 6WTT], U5G (PDB ID 6M0K), P6N (PDB ID 6YNQ), O6K (PDB ID 6Y2F), UED (PDB ID 6WTK), PK8 (PDB ID 6YT8), NOL (PDB ID 7C8T), X77 (PDB ID 6W63), 3 W L (PDB ID 6M2N), TG3 (PDB ID 7C8R), and N3 (PDB ID 6LU7) by percentage frequency. **(b)** Superposition of M^{pro} co-crystallized ligands (orange stick and ball represent the ligand N3, orange lines represent the other ligands) and amino acids of interaction within the active site of the M^{pro} (gray ribbons, white ball and stick).

Studies of MERS-CoV showed that RNA synthesis arrest installs three nucleotides after remdesivir is incorporated into the nascent RNA [39]. This suggests that RdRp is not the only viral protein to react against remdesivir, but that the nsp14 proofreader might detect a base pair mismatch after remdesivir is incorporated into RNA, thereby activating its exonuclease activity [40]. Hence, considering nsp14 in the design of nucleotide analogs against SARS-CoV-2 has been proposed [41].

Spike protein

The spike protein is a structural protein on the virion surface of coronaviruses and mediates the recognition by human cells through host surface receptors. Variations on this protein determine the histological tropism of the virus [42]. The S1 fragment binds to the host receptor, and the S2 fragment is then cleaved to promote membrane fusion, a process facilitated by host proteases, such as TMPRSS2, cathepsins, and furin [18,43,44]. SARS-CoV and SARS-CoV-2 spike protein binds to ACE2 [43,45], a transmembrane protease mainly expressed in the lungs, heart, kidneys, testes, and intestine [46]. Interestingly, and unfortunately, the affinity of SARS-CoV-2 spike protein to ACE2 is higher than that exhibited by SARS-CoV, mainly because of several residue changes at the interaction interface [47]. The fact that injection of SARS-CoV spike protein into mice worsened acute lung failure highlights the lung-protective properties of ACE2 [48]. Therefore, the administration of soluble ACE2 is also a potential treatment [49].

The crystallographic structure of the SARS-CoV-2 spike protein has been obtained in different conformations: uncleaved protein in the closed conformation (PDB ID 6ZGE); furin-cleaved protein in intermediate conformation (PDB ID 6ZGH), and furin-cleaved protein in the closed conformation (PDB ID 6ZGI). In addition, the 3D structure of ACE2 bound to the receptor-binding domain (RBD) of SARS-CoV-2 spike protein has also been elucidated at a 2.45 Å resolution (PDB ID 6M0J). The interaction among these last proteins comprises mainly polar interactions [45]. The large surface of the interaction site can be inhibited by monoclonal antibodies [50]. Nevertheless, experimental evidence for small molecules that directly block this protein–protein interaction has not yet been reported. Moreover, because of the high variability in glycans linked to the spike protein observed in other coronaviruses,

antigen recognition is expected to be challenging [51]. In addition, the spike protein shows high conformational freedom and undergoes large conformational changes that promote membrane fusion after binding ACE2 [51], making this site a challenging one to target as a therapy for COVID-19.

Furin

Recent data indicated that furin and TMPRSS2 activity is essential for virus proteolytic activation [52]. Furin belongs to the proprotein (also called prohormone) convertase (PC) family. These proteases are highly specific and are responsible for processing multiple precursors of proteins and bioactive peptides. Precursors are cleaved at the general motif (K/R)–(X)*n*–(K/R), where $n = 0, 2, 4,$ or 6, and X is any amino acid but usually not Cys [53].

Unlike SARS-CoV, the spike protein of SARS-CoV-2 contains a furin motif [54]. This structural difference appears to be responsible for its higher virulence, by increasing the activation of spike protein, thus facilitating entry into the host cell. Although this feature is not present in other beta-coronaviruses, the (K/R)-(2X)*n*-(K/R)↓ motif is present in human-infecting coronaviruses, such as OC43 and HKU1 [54]. Remarkably, the furin inhibitor decanoyl-RVKR-CMK also inhibits MERS and SARS-CoV-2 [18] and polybasic furin sites in hemagglutinin proteins are often found in highly virulent avian and human influenza viruses.

The furin motif in the spike protein of SARS-CoV-2 is a multibasic exposed loop: RNTR761 ↓ EV [55,56]. Cleavage of this motif breaks down the spike protein into the S1 and S2 sites. The S1 site contains the receptor-binding domain, which directly interacts with ACE2. The transmembrane site S2 facilitates fusion between the virus envelope and the host cell membrane surface [57]. Hoffman *et al*. showed that the S1/S2 site of SARS-CoV-2 is required for cell–cell fusion and that this can be potentiated by increasing the number of multibasic residues in the cleavage site [18]. This is in agreement with observations on the importance of the positive charge of furin inhibitors [58]. Notably, recent evidence showed that furin and other proprotein convertases have a role in inflammatory malignancies [59]. Therefore, targeting furin could be a way to contain viral infection and inflammation. By analyzing SARS-CoV-2 and human proteins associations, Gordon *et al*. identified 66 potential cellular proteins that, in addition to furin, could be targeted to prevent viral infection. Additionally, a SARS-CoV-2 protein interaction map that reveals targets for drug repurposing has been reported [60,61].

Drug repurposing for SARS-CoV-2

Drug repurposing is an attractive approach for swift access to COVID-19 therapy. For this endeavor, experimental and computational approaches can be used alongside the opinion of experts in clinical settings. Among the most commonly used computational approaches are those referring to signature matching (transcriptomic, proteomic, or metabolomic), chemical, and adverse event profiles, as well as genetic association, retrospective clinical analysis, and molecular docking [62]. Here, we present a strategy combining molecular docking vs with practical and clinical considerations.

Virtual screening of approved drugs

The accelerated pace of research and publishing on SARS-CoV-2, as reported in SciFinder, is overwhelming. From a total of 107,299 papers and preprint documents published at the time of writing, 1.18% relate to drug repurposing, and ~314 papers include computational methodologies (www.scifinder.cas.org, as of October 2020). In an exploratory analysis of the published documents focusing on repurposing drugs (peer-reviewed and preprints, a total of 462 documents), the most frequently mentioned drugs

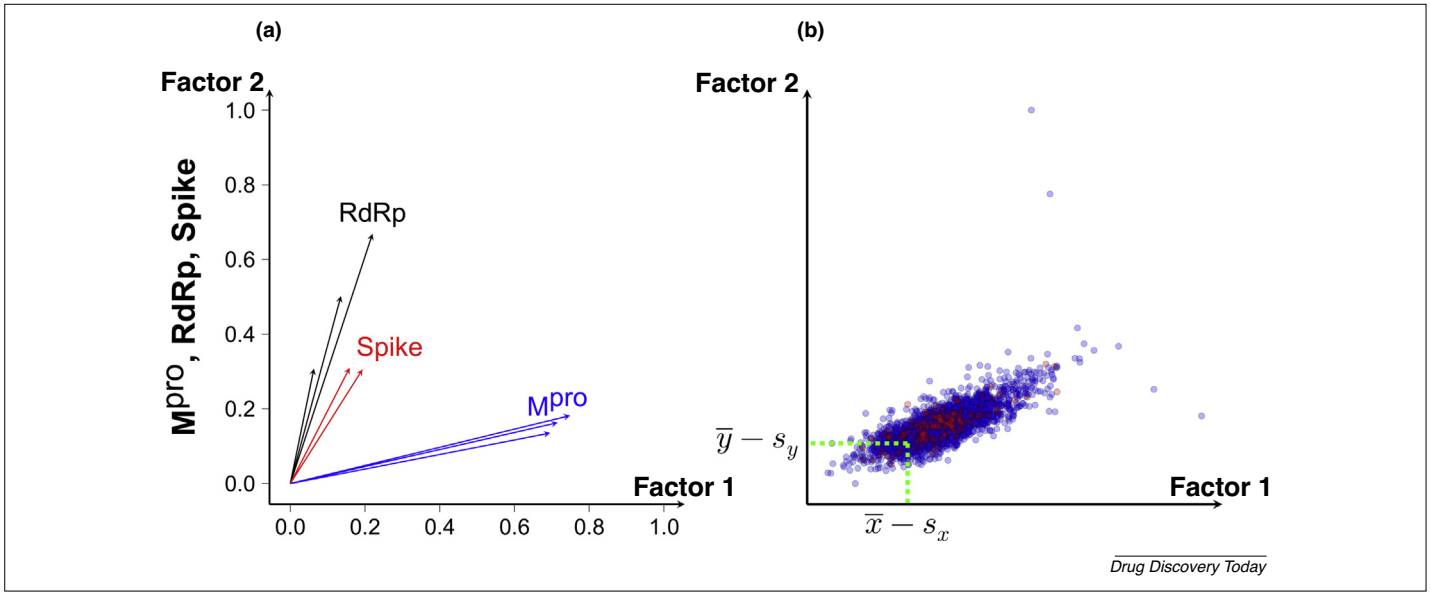

FIG. 3

Results from a factor analyses for the integration of ICM docking against M^{pro}, RNA-dependent RNA-polymerase (RdRp), and spike protein. **(a)** Configuration loadings for factor 1 and factor 2 are represented as vectors. Although a third factor was extracted in this case, it lies orthogonal to the plane and is not represented. **(b)** Molecules screened are mapped into the space defined by factor 1 and factor 2; red dots represent molecules with registered clinical trials against Coronavirus 2019 (COVID-19), and green rectangles outline the consensus subset of molecules. See Tables S4 and S6 in the supplemental information online for more details on factor loads and consensus thresholds, respectively.

were remdesivir (12%), lopinavir (9%), chloroquine (8%), hydroxychloroquine (8%), ritonavir (7%), quercetin (7%), darunavir (7%), favipiravir (3%), luteolin (3%), and curcumin (2%). To contribute to the search for efficient therapies, we performed a computational and literature-based drug repositioning strategy for the selection and proposal of potential drugs against COVID-19, with emphasis on dual therapies.

Approved drugs by the FDA (1332) and other international regulatory agencies (1946) (3278 molecules in total) were virtually screened with two docking programs (ICM and MOE) (see the supplemental information online for more details). Docking scores were integrated and studied with exploratory factor analysis, a statistical method used to describe variability among correlated variables, similar to principal components analysis but with better interpretability of the axes, termed factors. Figures S1 and S2 and Tables S1–S6 in the supplemental information online summarize the results from factor analyses of M^{pro}, RdRp, spike protein, and furin. As an example, Fig. 3a depicts the results of factor

TABLE 1

Top-ranked compounds from factor analysis of vs of approved drugs on each target of COVID-19 (M^{pro}, RdRp, spike protein, and furin)[a]

Drug (database)	Factor 1	Factor 2	Factor 3	Price (US$)	Antiviral evidence	In COVID-19 clinical trial?
Top-ranked hits with M^{pro}						
Lymecycline (not FDA)	−55.10	−204.43	N/A	$23.11	Indirect from other tetracyclines	No
Bromocriptine (FDA)	−53.47	−203.17	N/A	$0.32	Dengue, Zika	No
Thymopentin (not FDA)	−49.89	−287.86	N/A	NA	Herpes simplex virus (HSV), human papilloma virus (HPV)	No
Folic acid (FDA)	−43.22	−184.39	N/A	$1.38	Zika	Yes
Ceftazidime (FDA)	−39.14	−187.98	N/A	$4.44	HIV	No
Nystatin (FDA)	−34.43	−189.58	N/A	$15.16	HIV	No
Top-ranked hits with RdRp						
Lymecycline (not FDA)	−36.63	−1.30	0.04	$23.11	Other tetracyclines have antiviral effect against dengue, as well as anti-inflammatory properties	No
Ganciclovir (FDA)	−28.43	−2.48	−0.70	$64.44	Cytomegalovirus (CMV), hepatitis B virus (HBV)	No
Top-ranked hits in ICM docking consensus with M^{pro}, RdRp, and spike						
Thymopentin (not FDA)	−77.56	−58.59	−39.44	NA	HSV, HPV	No
Lymecycline (not FDA)	−75.61	−51.12	−40.71	$23.11	Other tetracyclines have antiviral effect against dengue, as well as anti-inflammatory properties	No
Tetracycline (not FDA)	−70.16	−46.01	−51.40	$1.56	Ebola, HIV	No
Folic acid (FDA)	−65.40	−55.06	−37.84	$1.38	Zika	Yes
Amiloride (FDA)	−62.78	−50.79	−45.40	$2.18	SARS-CoV	No
Luteolin (not FDA)	−59.73	−50.02	−45.37	$11.38	SARS-CoV-2, dengue, Influenza A, HBV, Dengue, Chikungunya	No
Famotidine (FDA)	−57.42	−35.38	−33.04	$10.18	SARS-CoV-2, HIV	Yes
Methotrexate (FDA)	−55.21	−41.00	−34.51	$22.18	Zika, Chikungunya	Yes
Ciprofloxacin (FDA)	−53.26	−39.42	−33.56	$5.87	Polyoma BK virus	No
Minocycline (FDA)	−52.51	−41.12	−35.18	$24.58	West Nile virus	No
Aminosalicylic acid (FDA)	−51.07	−46.17	−39.57	$1.51	None	Yes
Ketoprofen (FDA)	−51.06	−37.97	−33.95	$3.47	HCV	No
Prazosin (FDA)	−49.98	−35.15	−31.01	$7.16	None	Yes
Nitazoxanide (FDA)	−47.79	−40.33	−34.99	$2.31	MERS-CoV, Ebola, HBV, HCV, Chikungunya, Japanese encephalitis virus, astrovirus	Yes
Pentoxifylline (FDA)	−46.67	−34.97	−33.23	$5.47	HIV	Yes
Top-ranked hit with furin						
Lymecycline (not FDA)	−11.62	−27.39	N/A	$23.11	Other tetracyclines have antiviral effect against dengue, as well as anti-inflammatory properties	No
Top-ranked hits with spike protein						
	ICM average	Molecular operating environment				
Lymecycline (not FDA)	−19.01	−6.17		$23.11	Other tetracyclines have antiviral effect against dengue, as well as anti-inflammatory properties	No
Rivaroxaban (FDA)	−18.21	−5.86		$81.78	None	Yes
Telmisartan (FDA)	−14.67	−6.19		$10.80	Chikungunya	Yes

[a] Only compounds with accessible price, *in vitro* antiviral evidence, or that are undergoing COVID-19 clinical trials are shown. See Table S7 in the supplemental information online for related references and further details.

analysis integrating ICM docking scores against the three viral targets studied (M^{pro}, RdRp, and spike protein). Docking scores across repetitions were correlated, showing good reproducibility of the results. Moreover, docking across the different targets was distinctive (Figure S1 in the supplemental information online). Mapping of the molecules into the spaces defined by the factors is shown in Fig. 3b, where a green-dotted line represents a threshold (one standard deviation better than the mean) defined from the factors to select a subset of compounds that have better scores than the average of all factors, named here as consensus hits. For comparison, the co-crystalized ligands in M^{pro} are highlighted as orange squares, and in furin as a yellow triangles, in Figure S2 in the supplemental information online.

Molecules within the thresholds were annotated with their experimental antiviral evidence and information about ongoing clinical trials against COVID-19 from the scientific literature and the clinicaltrials.gov website. Thus, in addition to the analysis of structural information of selected viral and host molecular targets, we focused on a detailed analysis of pharmacological data, adverse effects, clinical evidence, price, and commercial availability of the drugs. These criteria trimmed down the number of computational candidates to those listed in Tables 1 and S7 in the supplemental information online. We recommend these criteria in virtual screening endeavors.

As observed from Table 1, several candidates are promising in the treatment of COVID-19. Of these potential candidates, two are particularly attractive for the treatment of COVID-19: lymecycline and famotidine.

Lymecycline

Lymecycline, a tetracycline drug, appears as the best hit in this screening, with the potential to bind to M^{pro}, spike protein, RdRp, and furin. Although no direct evidence of antiviral activity for this drug has been reported, other tetracyclines have antiviral and anti-inflammatory properties [63,64]. These results are in agreement with other docking studies reported in the literature [63–65]. Lymecycline is clinically attractive because of its high oral bioavailability; a half-life that allows the administration in a once a day scheme; readily accessible at low prices (in Mexico); and few adverse effects. Docking models for lymecycline into M^{pro}, spike protein, RdRp, and furin, as well as famotidine into M^{pro}, are depicted in Fig. 4.

Famotidine

Famotidine is an H2 antagonist and antiulcer agent with an optimal safety profile. *In silico* studies [66,67] revealed famotidine as a potential therapeutic agent against SARS-CoV-2 M^{pro} [65,66]. Another study indicated that its effect is not the result of antiviral activity, but an anti-inflammatory action. This drug has a good safety profile compared with other treatments that have been suggested for COVID-19. Most importantly, evidence for its efficacy was reported in a retrospective analysis and a prospective observational study [63,68,69]. However, controlled clinical trials are needed to measure the efficacy of famotidine as a therapy against COVID-19. Interestingly, we found famotidine to have good docking profiles in the consensus analysis of M^{pro}, spike protein, and RdRp. The best docking results of this drug were against M^{pro}, and a proposed binding mode of famotidine into the M^{pro} binding site is shown in Fig. 4d.

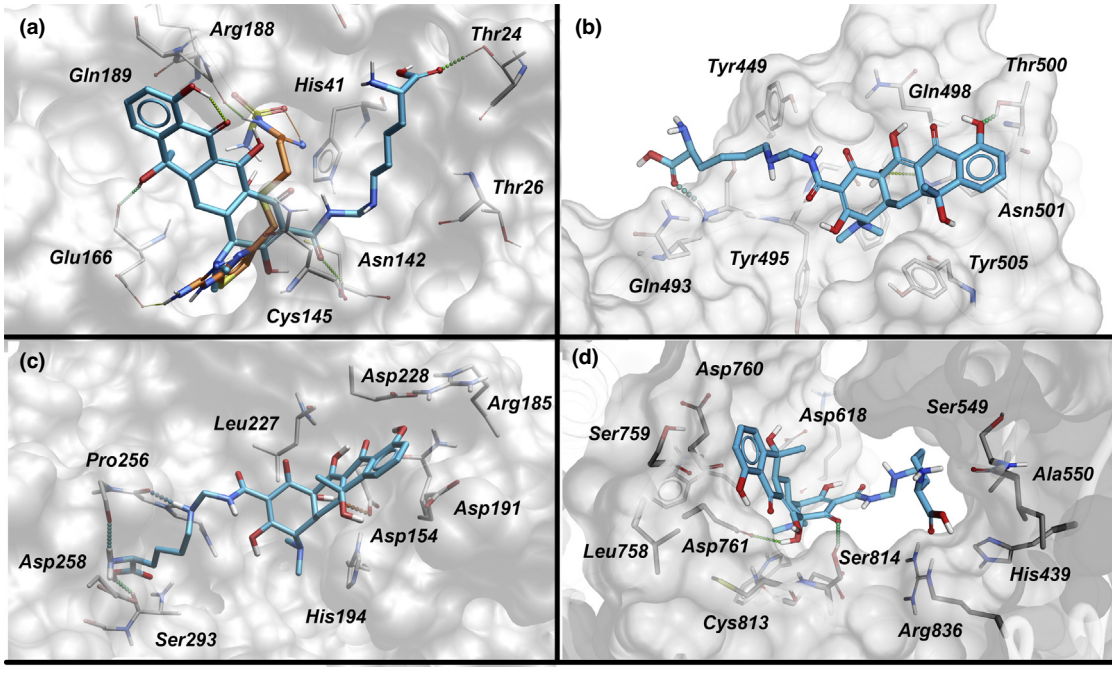

FIG. 4

Docking models for lymecycline (blue sticks) into **(a)** M^{pro}; **(b)** spike protein; **(c)** furin; **(d)** RNA-dependent RNA-polymerase (RdRp); and **(a)** for famotidine (orangesticks) into M^{pro}.

TABLE 2

Selected compounds to repurpose for use against COVID-19

Molecule	Targets predicted by docking	*In vitro* evidence of targets (from DrugBank)	Antiviral or anti-inflammatory evidence	Common adverse effects	Price in US$[d]	Ongoing clinical trials against COVID-19	Refs
Lymecycline	M^{pro}, spike protein, RdRp, furin	30S ribosomal subunit	Other tetracyclines have antiviral effect against dengue, as well as anti-inflammatory properties	Gastrointestinal disorders	$23.11	5 (all with doxycycline, from the same drug family)	[65]
Ivermectin	Spike protein[b]	GLRA3, GABRB3.	SARS-CoV2, other RNA viruses	Body temperature increased, loose stools, headache	$6.49	32	[77,85]
Famotidine	M^{pro}	HRH2	SARS-CoV2	Headache	$10.18	2	[63,68]
Curcumin[a]	M^{pro}, Spike protein[c]	PPARG, VDR, ABCC5, CBR1, GSTP1	Pleiotropic activity, including antiviral and anti-inflammatory properties	None reported	$35.00	1	[86]

[a] Curcumin was not tested as part of this drug repurposing study; nonetheless, docking results predict a plausible role as an M^{pro} inhibitor [81].
[b] Results from [79].
[c] Results from [80,81].
[d] By box or bottle.

Considerations from a medical perspective

Several clinical and preclinical studies are currently ongoing for the identification of relevant targets and therapies against COVID-19 (https://clinicaltrials.gov/ct2/results?cond=COVID-19). For instance, camostat mesylate, a TMPRSS2 inhibitor, was proposed as a potential treatment against COVID-19 [70]. In addition, the use of bromhexine (BHX), also an inhibitor of TMPRSS2, reduces mortality and complications resulting from COVID-19 [71]. Regarding the proinflammatory state and cytokine storm promoted by SARS-CoV-2, anticoagulants and dexamethasone have been proven useful as treatment and as secondary prophylaxis, reducing mortality in patients with severe COVID-19, at least in preliminary studies [72,73]. Anticoagulation led to diminished overall mortality in a prospective study of 2773 hospitalized patients, showing greater benefit in patients requiring mechanical ventilation [74]. Nonetheless, even under anticoagulation, patients severely ill with COVID-19 tend to develop thromboembolic complications [75]. Preliminary findings indicate that dexamethasone significantly reduced mortality in patients undergoing mechanical ventilation, but did not affect other subgroups of patients [76].

Once SARS-CoV-2 invades the body, immune cells secrete cytokines to initiate the immune response. However, immune cells continue to secrete cytokines even after enough immune response has been mounted. This process is known as a 'cytokine storm', and leads to an excessive and destructive inflammatory response in the body that produces serious clinical manifestations, such as severe respiratory distress syndrome. Inadequate treatment of the inflammatory response in patients with COVID-19 might explain the limited effectiveness of therapy directed unidirectionally to the antiviral load. Thus, drugs with different mechanisms of action should have better performance, such as by inhibiting at least one viral target and simultaneously preventing the cytokine storm through human targets. If early treatment is available, it could help prevent the cytokine storm and complications derived from it.

Our review of potential treatments that have been suggested for COVID-19 and our own clinical experience, lead us to two other interesting candidates for COVID-19: ivermectin and curcumin.

Ivermectin

Ivermectin is a semisynthetic anthelmintic drug that binds with high affinity to glutamate-gated chloride ion channels in invertebrate muscle and nerve cells of the microfilaria. Ivermectin also has anticancer and antiviral activities. *In vitro* studies revealed the antiviral activity of ivermectin against Zika, dengue, Newcastle, and chikungunya viruses, among others [77], attributed to the inhibition of nuclear importins in mammalian cells, which, in turn, hinder viral replication [78]. A recent study showed that ivermectin inhibited the RBD of the viral spike protein [79], has good bioavailability, a low price, and few adverse effects [80,81].

The potential benefit of ivermectin in the treatment of COVID-19 has been questioned, given that high doses would be required to achieve the concentrations that are linked to antiviral effects *in vitro*. This kind of extrapolation is not always valid, because other factors can contribute to the effect of the drug; only randomized clinical trials could exclude or ascertain its effectivity in patients. It

appears likely that a better strategy would be to test combinations of these small molecules with other compounds acting in different pathways related to COVID-19 clinical outcomes.

Curcumin

Curcumin is a natural product with potential use in the prevention and treatment of COVID-19. It has been described that a high intake of turmeric (*Curcuma*) in the diet has beneficial effects against inflammation, apoptosis, and RNA replication. Suppression of pulmonary edema and fibrosis-associated pathways in COVID-19 infection has also been reported [82]. Curcumin derivatives inhibit human A influenza virus *in vitro*, and docking studies propose curcumin as a potential inhibitor of spike protein binding to ACE-2 [80], as well as of M^{pro} [81]. Moreover, *in vitro* studies showed that curcumin inhibits the cytokine storm, such as that observed in patients severely ill with COVID-19 [83]. In addition, it has been reported that curcumin can regulate the expression of both pro- and anti-inflammatory factors, such as interleukin (IL)-6, IL-8, IL-10, and cyclo-oxygenase 2 (COX-2), promoting the apoptosis of polymorphonuclear (PMN) cells, and scavenging reactive oxygen species, which exacerbates the inflammatory response [83]. The safety of this drug is not a concern, because it is well tolerated even if consumed at high doses [84]. However, high potential for treating viral infections, such as COVID-19, with curcumin is limited by its low bioavailability. Thus, several strategies have been used to increase such bioavailability, including the development of formulations to encapsulate the drug in different matrices. Nevertheless, curcumin and its novel crystalline and amorphous phases offer a safe way to enhance the overall health of patients with the added value of antiviral and anti-inflammatory effects.

Proposed dual therapies

The information analyzed in this paper leads us to suggest three combinations that could be used as early treatment of COVID-19: ivermectin with lymecycline; ivermectin with curcumin; and famotidine with curcumin. Clinical trials of these therapies are in progress. Other combinations with these compounds might also be useful in the treatment of COVID-19. Relevant information on these drugs is summarized in Table 2.

Our analysis benefits from molecular modeling studies and clinical experience. The list of computational candidates was trimmed down based on experimental evidence (*in vitro*, *in vivo*, or clinical studies), pharmacological information, toxicity, availability, and cost. The involvement of clinical decision-makers in the process of finding and selecting hits increases the probability of undergoing clinical testing of effective drugs. A pilot controlled clinical trial to obtain evidence of the efficacy and safety of the proposed treatments is in progress.

Concluding remarks

Here, we have reviewed the most studied molecular targets and biological mechanisms that could be exploited for developing treatments against COVID-19. Aside from viral replication, host-mediated inflammatory response has a prominent role in the development of serious complications of this disease. Moreover, we suggest three drug combinations as therapies for COVID-19. The selected compounds were analyzed from different perspectives, including their pharmacological profiles, potential modulation (using computational models) of viral or human targets, availability, cost, and few adverse effects. We identified lymecycline and famotidine as hits of our integrative analysis; ivermectin and curcumin are other interesting molecules to repurpose against COVID-19, considering the available scientific literature. Research is underway involving controlled clinical trials (clinicaltrials.gov) to test the efficacy of these treatments, as well as combinations thereof. Target patients would be those with mild to moderate COVID-19, and with no contraindications against the use of the proposed drug treatments.

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Conflict of interest

J.G-M., M.M-C., and J.P.S-P. are employees of Laboratorios Senosiain S.A. de C.V., which manufactures famotidine, among other products.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drudis.2020.10.018.

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