



Review Article

Antiviral drugs against severe acute respiratory syndrome coronavirus 2 infection triggering the coronavirus disease-19 pandemic

Rashed Noor*

Department of Microbiology,
School of Life Sciences,
Independent University
Bangladesh, Dhaka, Bangladesh

ABSTRACT

So far, lots of analyses have been conducted to invent the appropriate therapeutic targets for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The category and the strategies for treating the virus are described in this review together with mentioning some specific drugs. Of them, saikosaponin possesses affinity of the drug toward nonstructural protein 15 and the spike glycoprotein of the SARS-CoV-2. The nucleotide inhibitors such as sofosbuvir, ribavirin, galidesivir, remdesivir, favipiravir, cefuroxime, tenofovir, and hydroxychloroquine (HCHL), setrobuvir, YAK, and IDX-184 were found to be effective in binding to SARS-CoV-2 RNA-dependent RNA polymerase. From the antimalarial and anti-inflammatory category, chloroquine and its derivative HCHL have already been approved by the U.S. Food and Drug Administration for emergency treatment of SARS-CoV-2 infection. The other drugs such as favipiravir and lopinavir/ritonavir under the antiviral category, the angiotensin-converting enzyme 2 (the renin-angiotensin system inhibitors), remdesivir (RNA polymerase inhibitor) from antiviral category, cepharanthine from anti-inflammatory category, etc., have been pointed based on the previous literature published. Besides, the assessment of the drug repositioning candidates with the related targets is also significant for the viral mitigation.

KEYWORDS: *Drugs, severe acute respiratory syndrome coronavirus 2 infection, Therapeutic targets, Viral mitigation*

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INTRODUCTION

The ongoing pandemic caused by the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is the current public health emergency round the globe. So far, the virus caused around 372,000 deaths out of approximately 6.5 million infected cases [1]. Unfortunately, till date, there are no officially announced vaccines or antiviral drugs against SARS-CoV-2 infection. Since the current world is encountering a huge health crisis by the coronavirus disease-19 (COVID-19) viral infection, evolving new treatment against SARS-CoV-2 is crucial to maintain the public health sustainability [1-4]. This is now a question of time which drugs that can selectively bind and subsequently inhibit SARS-CoV-2 proteins. Therefore, the emergence of the Food and Drug Administration (FDA)-approved antiviral drugs is really needed to mitigate the fatality of COVID-19. However, caution is needed when extrapolating the antiviral activity of any drug in the testing times; otherwise, it may impose severe side effects [4-7]. The clinical and immunological characteristics of severe patients thus need to be thoroughly understood [8]. Lots of analyses of the possible candidate

therapeutic targets for SARS-CoV-2 have been conducted and the efforts to discover the potential drugs are noteworthy [9]. Since the new drug development is really a time-consuming process, drug repositioning may be the most effective solution during a pandemic disease outbreak [9]. The major focus of drug development greatly relies on the four structural proteins of SARS-CoV-2: spike (S) protein, envelope (E) protein, membrane (M) protein, and nucleocapsid (N) protein, among which the S protein is mostly focused since it promotes host attachment and virus-cell membrane fusion during the viral entry to trigger the subsequent infection [9,10].

Lots of informative reports on the antiviral drugs for SARS-CoV-2 have so far been published. The present review compiled the information and presented the important drugs which can be effective candidates for the elimination of COVID-19. The category and the strategies for treating

*Address for correspondence:

Dr. Rashed Noor,
Department of Microbiology, School of Life Sciences, Independent
University Bangladesh, Plot 16, Block B, Dhaka, Bangladesh.
E-mail: rashednoor@iub.edu.bd

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SARS-CoV-2, the target sites for the drugs, and the effectiveness of their potential to remediate the disease have been discussed.

STRATEGIES TO INACTIVATE SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 AND TO DEVELOP NOVEL DRUGS

The anti-coronavirus therapies can be divided into two categories largely based (1) on the human innate immune system and (2) on the virus itself [9-11]. Indeed, the innate immune system response plays a significant role in regulating viral replication and the host infection whereby a number of innate immune cells are likely to trigger the immune response [11,12]. Upon entry of SARS-CoV-2 into the respiratory tract, an orchestrated network between the airway epithelial cells, the alveolar macrophages, the innate lymphocytes, neutrophils and dendritic cells, the toll-like receptors 3, 7, and 8, and the pathogen-associated molecular patterns by the pattern-recognition receptors occurs to create an antiviral state along the lungs. However, the viral infection otherwise results in the increased leukocytes and the pro-inflammatory cytokines (i.e., the cytokine storm) such as the interleukin 1- β (IL1- β), the IL-1 receptor antagonist, IL-2, IL-7 to IL-10, granulocyte colony-stimulating factor (G-CSF), interferon- γ (IFN- γ) inducer protein 10, monocyte chemoattractant protein-1, the macrophage inflammatory protein-1 α (MIP-1 α), MIP1 β , tumor necrosis factor (TNF α), basic fibroblast growth factor-2, G-CSF, granulocyte-macrophage colony-stimulating factor, platelet-derived growth factor, and vascular endothelial growth factor A [8,12]. Therefore, blocking the signal pathways of human cells required for the SARS-CoV-2 replication may impart an antiviral effect [9]. For the second category of anti-SARS-CoV-2 therapy, the fact is projected through the viral binding to the receptor proteins, i.e., the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of cells in order to enter the human host cells [9,12]. The direct therapies on the coronavirus mainly include (1) preventing the synthesis of viral RNA, (2) inhibiting the viral replication, (3) blocking the binding of the virus particle to the host cell receptors, and (4) inhibiting self-assembly of the virus [9].

According to Wu and his coworkers, in order to develop novel antiviral drugs against coronaviruses, the *in silico* testing (i.e., computer simulation) of the existing broad-spectrum antivirals (IFNs, ribavirin, and cyclophilin inhibitors which are used to treat coronavirus pneumonia) in terms of the metabolic traits, drug dosage, assessment of potential efficacy, as well as the possible side effects is the first strategy [9,13]. However, since these drugs are the so-called "broad-spectrum" ones, they actually cannot eliminate coronaviruses in a targeted manner [9]. The second strategy may involve using the existing molecular databases for high-throughput screening special molecules imparting the therapeutic effects (identifying the new functions of the drug molecules) on coronavirus [9,14]. The third approach covers the concept of the viral genomics and the pathophysiological traits of different coronaviruses to create new targeted drugs; these types of drugs would demonstrate better therapeutic effects on the coronaviruses [9,15]. The whole genome sequencing of SARS-CoV-2 along with the

subsequent open reading frame (ORF) detection, predictions on the secondary and tertiary structure of the encoded proteins, assessment of the viral-binding sites to the host receptors, and the predictions on the potential microRNAs (miRNAs) has already unraveled eight ORFs, which in turn facilitated (1) the detection of binding sites between several drugs and the ORFs, (2) screening of several drugs through the sequence search module, and (3) the prediction of at least two miRNAs which can successfully prevent the replication of SARS-CoV-2 through targeting the 3'-UTR (untranslated region) of the viral RNA [15].

POSSIBLE ANTIVIRAL DRUGS TO MITIGATE CORONAVIRUS DISEASE-19 CAUSED BY SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

As stated above, no vaccine or FDA-approved drug is available to exterminate SARS-CoV-2; however, some drugs used for other viral illnesses such as malaria, Ebola, SARS, and Middle East respiratory syndrome may come in use of eradication of the infection to some extent [16]. Based on the literature, the drugs can be categorized into antiviral and anti-inflammatory drugs, the antimalarial drugs, the traditional Chinese drugs, and others [16]. However, intensive clinical trials and drug development research are in demand. The following are some important drugs which are currently being used to treat COVID-19 [Table 1].

Saikosaponin

The *in silico* assay showed that saikosaponin (a group of oleanane derivatives) possesses the anti-coronaviral property by interfering with the early stage of viral replication as well as hindering the absorption and penetration of the host by SARS-CoV-2 [2]. The drug was screened and its potency was evaluated against different sets of SARS-CoV-2-binding protein via computational molecular docking simulations (i.e., analyzing the nonstructural protein, NSP15) that is responsible for replication of RNA and the spike glycoprotein that is responsible for the connection with ACE2 by Sinha and his group very recently [2]. The studies on the binding energy and interaction revealed satisfactory affinity of the drug toward NSP15 and the spike glycoprotein [2].

Nucleotide inhibitors

Nucleotide inhibitors are known to be effective against different viral infections [3]. Recently Elfiky conducted another *in silico* assay using the viral protein RNA-dependent RNA polymerase (RdRp) and its binding affinity to some clinically approved drugs and drug candidates [3]. The computational data revealed the dynamics of the RdRp to understand how it affects the binding of the candidate drugs and the effectiveness of sofosbuvir, ribavirin, galidesivir, remdesivir, favipiravir, cefuroxime, tenofovir, and hydroxychloroquine (HCHL), setrobuvir, YAK, and IDX-184 in binding to SARS-CoV-2 RdRp [3]. The *in silico* analysis unraveled four novel IDX-184 derivatives to come up with nearly guaranteeing results in attaching to the SARS-CoV-2 RdRp [3].

Table 1: Major antivirals against severe acute respiratory syndrome coronavirus 2: Immunomodulation agents; antivirals targeting the viral life cycle; and the antivirals targeting the structural proteins

Antivirals	Category	Mode of action	Assay condition	References
Glucocorticoids	Immunomodulatory agent	Anti-inflammation	Clinical trials in patients	[8,16]
IL-6 antagonist	Immunomodulatory agent	Inhibition of the cytopathic effects	Clinical trials in patients	[8,16]
Baricitinib plus fedratinib plus ruxolitinib	Immunomodulatory agent	JAK inhibitors	<i>In silico</i> model	[19]
Cepharanthine plus selamectin plus mefloquine hydrochloride	Immunomodulatory agent	Inhibition of the cytopathic effects	Cell culture	[19]
Fedratinib	Immunomodulatory agent	JAK inhibitors	Cell culture	[18]
Lianhuaqingwen	Immunomodulatory agent and antiviral targeting the viral life cycle	Inhibition of cytokine storm; i.e., cytopathic effects; inhibition of viral replication	Cell culture	[17]
Chloroquine/ hydroxychloroquine	Immunomodulatory agent and antiviral targeting the viral life cycle	Inhibition of the cytotoxicity; immunosuppression; changing the glycosylation of ACE2 receptor and spike protein; nucleotide inhibitors	Cell culture	[4-6,16,31]
Camostat mesilate	Antiviral targeting the viral life cycle	TMPRSS2 inhibitor	Cell culture	[20]
Favipiravir	Antiviral targeting the viral life cycle	RdRp inhibitor; nucleotide inhibitors	Clinical trials in patients	[21]
Lopinavir plus ritonavir	Antiviral targeting the viral life cycle	Protease inhibitor	Clinical trials in patients	[22]
Remdesivir	Antiviral targeting the viral life cycle	RNA polymerase inhibitor; RNA chain terminator; nucleotide inhibitors	Cell culture	[23]
Ribavirin	Antiviral targeting the viral life cycle	Nucleotide inhibitors	<i>In silico</i> model	[3]
IDX-184 derivatives	Antiviral targeting the viral life cycle	Nucleotide inhibitors	<i>In silico</i> model	[3]
Saikosaponin	Antiviral targeting the structural protein	Binding to the spike (S) glycoproteins	<i>In silico</i> model	[2]
Arbidol	Antiviral targeting the structural protein	Inhibition of the membrane fusion	Cell culture	[2]
Hexamethylene amiloride	Antiviral targeting the structural protein	Inhibiting the E protein-linked ion channel activity	Cell culture	[32]
N220 peptide	Antiviral targeting the structural protein	Selective killing of the N protein expressing cells	Animal cells	[33]

Chloroquine and hydroxychloroquine: The promising antiviral drug

Chloroquine (CHL) and its safer derivative HCHL, the antiviral drugs that interfere with the glycosylation of the proteins (which in turn increase the endosomal and lysosomal pH), are impelled the active drug against SARS-CoV-2 [Figure 1], since CHL has been noticed to inhibit the virus in cell cultures as well reduced the viral load in the infected individuals [4-6]. This is to be mentioned that the USFDA has approved an emergency use authorization for use of HCHL for the COVID-19 treatment [4]. It is known that the acidic pH of endosomes and lysosomes helps in the fusion of the virus particles to the host cells with the concomitant release of their genetic material and hence the start of virus replication [4]. Modification of the viral protein glycosylation, thus, interferes with the assembly of new virus particles. Besides, CHL/HCHL are known to impart the anti-inflammatory activity in cell cultures; since the SARS-CoV-2 causes an acute inflammation in the lungs (which is central to the pathology of COVID-19), these drugs may have potential benefit too [4,7]. Another important point is to ponder that a nonrandomized open-label trial previously showed the reduction in the SARS-CoV-2 viral RNA load when the infected patients were treated with the mixture of HCHL and azithromycin [4,6]. Although the effect of CHL/HCHL on virus replication is of particular importance from a public health perspective, the injudicious application (overdose toxicity and fatal outcome of self-administration) of these drugs to treat COVID19 may rather trigger the disease severity [4,8].

ANTI-CORONAVIRUS THERAPIES BASED ON THE HUMAN INNATE IMMUNE SYSTEM: IMMUNOMODULATION

Glucocorticoids, IL-6 antagonist (Atlizumab Kevzara are the humanized monoclonal antibody against IL-6 to hinder the viral pathogenesis), the Janus kinase (JAK) inhibitors, and CHL/HCHL [Figure 1] exhibited improved clinical outcome while lianhuaqingwen, used African green monkey kidney epithelial cells and the human hepatocellular carcinoma cells were found to be protective against COVID-19 [16,17]. JAK2 inhibitor fedratinib may be beneficial in reducing cytokine storm associated with COVID-19 infection [16,18]. Based on *in silico* observation, the combination of baricitinib, fedratinib, and ruxolitinib is also predicted to be in significant beneficial effects in the treatment of COVID-19 [16]. The combination of three drugs, cepharanthine (CEP), selamectin and mefloquine hydrochloride, was found to be completely inhibitory of the cytopathic effects in cell culture at 10 $\mu\text{mol/L}$, among which CEP was noticed to be the most potent in cell culture [16,19].

DRUGS ACTIVE AGAINST SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 LIFE CYCLE

Camostat mesilate is a serine protease inhibitor which stops the initial viral infections (in cell culture) by binding to the transmembrane serine protease 2 (TMPRSS2) that primes

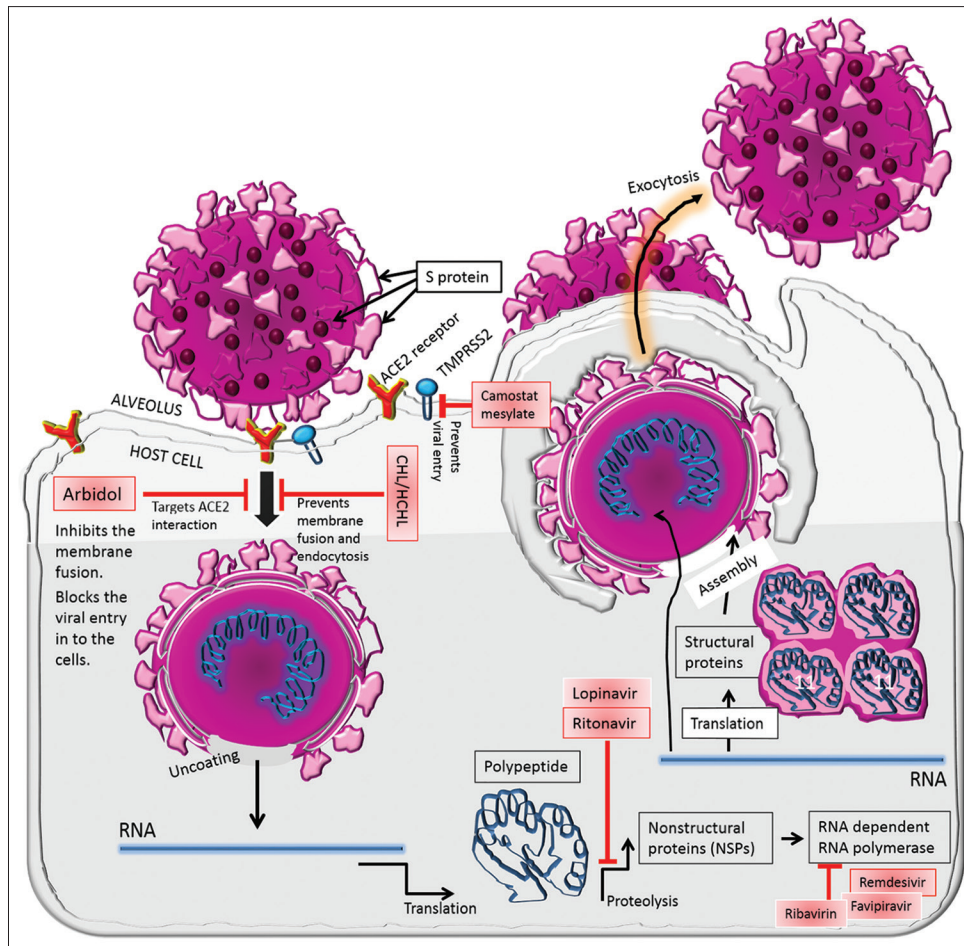


Figure 1: Some prominent antiviral drugs working against severe acute respiratory syndrome coronavirus 2. The mode of action of camostat mesilate, chloroquine/hydroxychloroquine, favipiravir, lopinavir, ritonavir, arbidol, remdesivir, and ribavirin has been elucidated

the spike protein of SARS-CoV [20]. In a patient trial study, favipiravir was found to significantly shorten the viral load possibly by binding to the RdRp [16,21]. Lopinavir plus ritonavir was found to improved clinical symptoms in a hemodialysis patient with COVID-19 pneumonia [16,22]. Lopinavir is a protease inhibitor; since the viral replication requires the action of viral proteases, lopinavir/ritonavir were found to be effective to inhibit the viral replication by binding to the protease [22]. Remdesivir (broad-spectrum RNA polymerase inhibitor antiviral drug) forms a complex and is likely to delay RNA chain termination [Figure 1]; the nucleotides may protect the inhibitor from excision. Such a situation may explain the high effectiveness of remdesivir against RNA viruses in cell-based assays [16,23].

Interestingly, Nguyen and his group (in 2020) proposed that CRISPR/Cas13d system may possess straightforward and flexible potentiality for RNA virus treatment and prevention which may be used for the treatment of SARS-CoV-2 infection [24]. As stated elsewhere, one of the most significant achievements in the anti-SARS-CoV-2 drug development has been the lopinavir/ritonavir which may significantly reduce the viral load in the infected individuals [16,25]. Among the antiviral and antimalarial drugs, remdesivir, ribavirin (nucleoside inhibitor and the guanosine analog that can be used to

truncate the viral RNA synthesis as well as the capping of the viral mRNA), penciclovir, nitazoxanide, nafamostat, remdesivir (an adenosine nucleotide analog, GS-441524, which interferes with viral the RNA-dependent RNA-polymerase and evades the proofreading activity by the viral exonuclease, ExoN, thereby decreasing the viral RNA production), favipiravir (selectively inhibits the viral RdRp; and induces lethal RNA mutations, producing a nonviable viral phenotype), and CHL, the remdesivir and the CHL [Figure 1] was found to be the most effective in cell culture assay [5]. Among the others falling in the same category, lopinavir/ritonavir (protease inhibitor), and Shufeng Jiedu (Chinese med) was also found effective to eliminate the virus using cell culture assay [16,26].

INHIBITORS OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 STRUCTURAL PROTEINS

Prajapat *et al.* conducted a systematic review based on PubMed and RCSB database; they identified the viral structural proteins as the possible targets for action by the antiviral drugs [10]. However, as stated earlier, the S protein is of the major focus since the viral entry it facilitates the viral entry using its receptor-binding S1 domain (three S1 heads) and the membrane fusion subunit S2 (trimeric stalk) on the C-terminal

end of its ectodomain region [9,10]. Initial interactions between the S1 receptor-binding domain (RBD) and the host receptor ACE2 followed by the subsequent S2 segment mediated fusion of the host and viral membranes allow the viral genome to enter inside the host cells, and hence, these proteins are the most important targets among all the structural proteins from the drug discovery aspect [27].

Angiotensin-converting enzyme 2 inhibitors

The anti-ACE-2 antibody was found to block the viral entry and replication in Vero E6 cells [10]. Indeed, among all the structural proteins, the most important drug target is the ACE2, which can be fused to an immunoglobulin Fc domain [16]. ACE2-Fc is known to possess the potentiality to be the neutralizing antibody, which in turn can be used for inactivating the virus [28]. An interesting work has been conducted by Fan and his group whereby they screened the clinically approved drugs for anti-coronavirus activity of SARS-CoV-2-related coronavirus model and identified the potent inhibitors for pangolin coronavirus infection [22]. It is well known that ACE2 is the cell receptor for SARS-CoV, bat SARS-like CoV, and SARS-CoV-2 [29,30]. This group noticed that ACE2 expression can be knocked down by siRNA, which actually urges the necessity of the study of genomics level to alleviate the COVID-19 onset [9,15,22]. As stated earlier, through the computational analysis, the drug saikosaponin has been found to possess the capacity to bind to the spike (S) glycoproteins, which in turn may block the viral entry (2). However, arbidol was found to inhibit the membrane fusion in cell culture, hence the restriction of the viral entry in to the host cells too [16].

Besides ACE2, the RBD has also been reported as a prime target in the other drug-designing studies too [10,29]. A peptide sequence consisting of a similar sequence to that of RBD (for S protein binding) was noticed to be hindered (i.e., the S1-RBD: ACE-2 interaction was blocked), thereby preventing the viral into Vero cells [10]. The *in silico* study showed that hesperidin (hesperetin 7-rutinoside), a flavonoid compound, has been reported to block the interface of ACE2 and spike RBD binding and hence hinders the viral spike-ACE2 interaction, which in turn may prevent the viral entry [9]. CHL has been noticed to inhibit the terminal glycosylation of ACE-2 and hence interrupting the RBD: ACE-2 interaction in the Vero E6 cells (an African green monkey kidney cell line) [10,31].

Inhibitors of other structural proteins

Amiloride has been found to block the E protein-associated ion channel activity in the mammalian cells [10,32]. Regarding the inhibition of M protein, a study showed that the mice vaccinated with the SARS-M DNA had achieved the appropriate T-cell immune response together with the cytotoxic T-cell response against the SARS-DNA-transfected alveolar epithelial cells [10]. The peptides N220, NP111, NP331, and NP351 were found to be targeting the viral N protein, among which N220 showed the trait of selective killing of the N protein expressing cells in transgenic animals and hence is a potential candidate for DNA vaccine [10,33].

DRUG REPOSITIONING

Screening of the drug-repositioning candidates with the corresponding targets of SARS-CoV-2 is important for the viral alleviation. Wu and his group conducted *in vitro* and *in vivo* studies on the new candidate drugs with their corresponding targets within SARS-CoV-2 and proposed the suggestive evidence of drug repositioning to treat the infected individuals [9]. They analyzed all the SARS-CoV-2 proteins with subsequent comparison with other coronaviruses, projected their structures, and finally built 19 structures (the SARS-CoV-2 targets) and 1 human target by means of homology modeling [9]. Twenty-one targets (including two human targets) were screened by performing the target-based virtual ligand screening; the major targets including 3-chymotrypsin-like protease (3CLpro), spike protein, the RdRp, and the papain-like protease (PLpro) have been discussed [9]. Besides, a database of 78 commonly used antiviral drugs (screened against the 19 SARS-CoV-2 targets plus human ACE2) by Wu and his groups was constructed; the possible targets of these drugs were predicted [9]. This is to be noted that considering the high pathogenicity and transmissibility of SARS-CoV-2, working with the live viruses must require high-level biocontainment facilities [27].

CONCLUSION

The current review enlisted the important drugs which may be effectively potential to mitigate the COVID-19 infection. Indeed, all the drugs discussed here are currently under trial, and most of them have been found to be effective against SARS-CoV-2-infected patients. Especially, remdesivir, CHL/HCHL, ribavirin, favipiravir, CEP, and lopinavir/ritonavir evolved with potential antiviral activities against the SARS-CoV while saikosaponin, IDX-184, and the other ACE2 inhibitors as revealed from the *in silico* study, can also be effective in mitigating the disease.

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Conflicts of interest

There are no conflicts of interest.

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