Review Article



# Comprehensive review on the prevailing COVID-19 therapeutics and the potential of repurposing SARS-CoV-1 candidate drugs to target SARS-CoV-2 as a fast-track treatment and prevention option

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**Abstract:** The recent seemingly uncontrollable pandemic caused by the novel severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) has been able to spread quickly due to the non-availability of effective antivirals or vaccines. The virus has structural and non-structural proteins that are considered as possible targets. Receptor recognition is the critical determinant and preliminary phase of viral infection to enter the host cell and causes tissue tropism. We have conducted a comprehensive review of relevant publication on *in vitro*, *in silico*, *in vivo* and clinical evaluation of drug candidates ranging from broad-spectrum antivirals to natural molecules targeted towards viral spike protein in addition to evaluate their suitability as therapies based on an analysis of the similarities between SARS-CoV-1 and SARS-CoV-2. In general, antiviral targets are based on two strategies, either targeting the host or the host's immune cell. We have reviewed the available details on the SARS-CoV-2 strain's host-viral binding sites entry mechanism, alongside recently tested effective antivirals. The hypothesis of this review may provide clear insight for researchers and physicians who are struggling to narrow down scientific options to control the current pandemic. Overall, we found that the promising efficacious drug candidates reported against SARS-CoV-1 could be considered for drug repurposing; this might help to identify a potential drug for therapeutic measures and development of vaccine for COVID-19.

**Keywords:** Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2); COVID-19; antivirals; SARS-CoV-1; repurposing

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## Introduction

The term novel virus called severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), has been officially designated to replacing the term human coronavirus 2019 (HCoV-19) mentioned by the International Committee on Taxonomy of viruses (1). The disagreement of surrounding the term HCoV-19 resulted in the committee's recommendation to name as human coronavirus due to its less pathogenicity but faster spread than SARS-CoV-1 (2). The genome has already sequenced, enabling researchers to pinpoint its origin from bat through phylogenetic mapping and also identifying Pangolins as the intermediate host between Bats and Humans; but not mice or rats. COVID-19 has spread through more than 100 countries, with over 100,000 confirmed cases and 3,800 confirmed deaths worldwide at the beginning of March (3), and three month later, the high-risk global death toll has extended up to 507,435 with 10,321,689 confirmed cases as reported at the end of June by WHO (4). The rapid spread of the communicable disease, was determined based on the high reproductive number [$R_0$] of SARS-CoV-2. The R-naught [$R_0$] is a mathematical measure to determine the average number of people the disease has spread from a contagious person. Initially the WHO has set the $R_0$ at 1.4–2.5 but later it was revised as being 4.7 and 6.6 $R_0$ (5).

The crippling illness attached to COVID-19 infection have emerged as a drastic challenge to world health made worse lack of a vaccines or effective antiviral drug which could prevent or effectively cure the disease. Therefore, we aim to provide an update on drug candidates for antiviral efficacy and potent vaccines to SARS-CoV-2 and offer insights on the advantage of repurposing, drug candidates of antivirals and vaccines for SARS-CoV-1 to SARS-CoV-2. Many studies, namely *in silico* and *in vitro*, have been undertaken to develop therapeutic agents, and few have advanced up to preclinical and clinical trials on SARS-CoV-2 infections. We have placed a special focus on updating on the potent and non-potent antivirals in a nutshell for the researchers and clinicians to promote further progress in developing highly safe and potent drugs to treat COVID-19 infection successfully. More than 500 journal articles have been published since the SARS-CoV-2 outbreak, in which nearly 80 of which address the scope of effective repurposing of antivirals (3). Within the short period of outbreak, few reviews/systematic reviews have also been published (6-10). There has been more focus on the usefulness of lopinavir and chloroquine has been published (11,12). However, our review provides an update of all trialled antivirals based on their mode of action, it also emphasis their repurposing as potential anti-SARS-CoV-2 therapy. We excluded MERS or any other coronavirus species in terms of similarity of SARS-CoV-2 as only observed with SARS-CoV-1, especially in binding with the similar receptor and entry mechanism. The discussed similarity provides the possibility of repurposing drug candidates of SARS-CoV-1 to SARS-CoV-2. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4071).

## Current management of SARS-CoV-2 associated complications

When WHO declared COVID-19 disease as a global pandemic, multiple strategies on control measures such as strict physical distancing and hygienic measures were implemented by the affected countries around the world, to reduce the R° and mortality rate of SARS-CoV-2. The WHO recommended specimens such as blood cultures, upper respiratory tract, nasopharyngeal or oropharyngeal swabs were collected for RT-PCR testing where the expectorated sputum, endotracheal aspirate or bronchoalveolar lavage are later tested for positive COVID-19 infection to observe any diversified clinical symptoms (13). The most practised strategies to avoid community spread were isolation at home, quarantine measures following any travel, the lockdown on any mass gathering, and the request to maintain social distancing of 1.5 metres. The pharmacological approach depended on each country's preference, but predominantly, chloroquine and hydroxychloroquine (HCQ) were widely used at the beginning, which has been approved by the FDA as a prophylactic drug (14,15). Within a short time, FDA has not issued the usefulness of HCQ for COVID-19 disease due to its severe side effects namely increasing heart rate, renal failure and heart attack reported in the pre-clinical trials conducted in USA. However, FDA has authorized

 

for 800 mg intake on the first day to 50 kg or more weighed patients (16). Later, on observing the risk from large randomised clinical trials, FDA has withdrawn the approval for COVID19, however the FDA approval status for malaria, lupus and Rheumatoid arthritis will not be affected (17). China predominantly focussed on managing respiratory support and the treatment ailments as per the National Health Commission of the people's Republic of China (18). The WHO recommended the provision of extracorporeal membrane oxygenation to critical patients with distress and refractory hypoxemia, and also high flow nasal oxygen and non-invasive ventilation has been provided for hypoxemia patients (13). In addition, endotracheal intubation was recommended for obese and pregnant patients.

## Pathogenesis and clinical manifestation

Similar to SARS-CoV-1 and Middle Eastern respiratory syndrome (MERS), SARS-CoV-2 consists of structural (spike, M and nucleocapsid) and non-structural proteins (3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase), which may act as susceptible viral targets (19). Human angiotensin-converting enzyme 2 (ACE2) is a host receptor that acts as a functional receptor and facilitates binding with the spike proteins to adopt prefusion conformational changes. Since ACE2 is expressed in many tissues such as lung, liver, heart, gastrointestinal tract and kidney, the virus can rapidly invade the body cells through this receptor and replication leads to manifest clinical symptoms (19).

COVID-19 patients show the symptoms such as fever, cough, dyspnoea, and in severe cases, may lead to the acute respiratory syndrome, pneumonia, fibrosis, renal failure, and death in high critical cases. Impaired immunity and lymphopenia are essential characteristics symptoms which upregulates, C-reactive protein (CRP) as it can be considered as significant diagnostic biomarker for COVID-19 disease (20). The predominant clinical symptom 'pneumonia' was observed in many patients, presented in Chest CT scan, and the abnormal features such as RNAaemia, acute respiratory distress syndrome, acute cardiac injury, and incidence of grand-glass opacities possibly lead to death as a primary endpoint (21). The incubation period of SARS-CoV-2 is 5.2 days, while 6 to 41 days is usually for the onset of critical clinical symptoms. Patients with afebrile and absence of dyspnoea may recommend for CRP count and guidance for self-isolation. The chest CT reveals patchy infiltration for positive patients (20).

## Association between SARS-CoV-2 and SARS-CoV-1

### *Similarities and dissimilarities of SARS-CoV-1 and SARS-CoV-2*

Based on genomic analysis, SARS-CoV-2 belongs to the Beta coronavirus genus of the Coronaviridae family, positive-sense, single-stranded RNA consists of 29,900 nucleotides encoding structural and non-structural proteins (22). The human coronaviruses have been studied since 1960, and the current outbreak causing SARS-CoV-2 is the seventh species of the Coronaviridae family that infect humans (23). Among these, NL-63, 229E, HKU1 and OC43 cause mild illness, while SARS-CoV-1, MERS-CoV and SARS-CoV-2 have led to severe life-threatening pandemic illness (24). Out of these three, SARS-CoV-1 and SARS-CoV-2 share the same entry mechanism and receptor called ACE-2, which is an essential residue for the binding site of these viruses, whereas MERS-CoV binds to the receptor dipeptidyl peptidase 4 (25). Since SARS-CoV-1 and SARS-CoV-2 bind to the same human receptor, viral entry could be considered as an essential target for predicting the utility of currently used antivirals. The spike protein is the main key for entry into host-cell through ACEII receptor on priming with other co-factors. Therefore, effective SARS-CoV-1 therapies targeted to the entry site could be explored for use in identifying potent antivirals to inhibit SARS-CoV-2 multiplication.

Homology modelling demonstrates 80% similarity between SARS-CoV-1 and SARS-CoV-2 (26). In particularly the spike protein of SARS-CoV-1 and SARS-CoV-2 shares 75% similarity towards amino acid sequence (27). The SARS-CoV-2 binds with stronger affinity to the ACE receptor than SARS-CoV-1, with maximum proximal similar amino acid residues (22). The ACE receptor is membrane-associated aminopeptidase that consists of a high level of viral regulatory genes which are involved in the viral life cycle. *Figure 1* represents the mechanism of entry and possible targets for SARS-CoV-2.

Grifoni *et al.* compared the protein sequence through a homology modelling and bioinformatics approach. They demonstrated that SARS-CoV-1, MERS-CoV and bat-SL-CoVZXC21 revealed the similarities with SARS-CoV-2 as

76%, 35% and 80% of the spike protein respectively (28). Among the different strains, bat-SL-CoZXC21, non-human strain was showed highest similarity. SARS-CoV-1 spike protein has expressed as highest similarities than MERS-CoV. The authors have reported the B cell epitopes sequencing of SARS-CoV-2 and SARS-CoV-1 regions from immune epitope databases and studied the Spike proteins similarities, where the resemblances were ranging from 69–100%. In addition the study has reported sequencing ORF1ab (86%), E (94%), M (90%), N (90%), S (76%) to find the protein similarities of SARS-CoV-1 with MERS-CoV as ORF1ab (50%), E (36%), M (42%), N (48%), S (45%). In addition, the study compared B and T cell immunodominant SARS-CoV-1 was mapped to the homologous SARS-CoV-2 proteins and found to have a high percentage of similarity (28).

Kumar *et al.* studied the spike protein sequence of SARS-CoV-2 with SARS-CoV-1 using EMBOSS Needle pairwise sequence alignment tools (29). The authors revealed that 12.8% of difference observed in the S protein between both strains, especially in the amino acid sequence alignment. In addition, 83.9% similarity was observed in the minimal receptor-binding domain (RBD) with SARS-CoV-1. The RBD of SARS-CoV-2 has 73% similarity with SARS-CoV-1 RBD (30). The phylogenetic analysis study has revealed the overall sequence similarities for SARS-CoV-1 and SARS-CoV-2 for around 76–78% for the whole protein, 73–76% for the RBD, and 50–53% for the RBM (22). The Sequence alignment between SARS-CoV-1 (RBD219-N1) and SARS-CoV-2 spike protein has shown 75% identity and 83% similarity in RBD region (31). Therefore, based on these similarities, our review has focussed on the antivirals used to treat SARS-CoV-1 that could be considered for use against SARS-CoV-2.

The significant dissimilarities between these SARS-CoV-1 and SARS-CoV-2 occur in the genomic material, non-structural proteins and in nucleocapsid. The open reading frame of SARS-CoV-2 was sequenced and compared with the SARS-CoV-1 viral genome, and a mutation was observed in the non-structural proteins (NS2 and NS3). The observed destabilising mutation may be the reason for the rapid spread and seriousness of the infection (32). The comprehensive support on the difference between these two strains has been observed in non-structural and accessory proteins. They are similar in non-structural protein alignment but vary in structural amino acids. For instance, SARS-CoV-2 does not contain 8a protein but has a long amino acid chain with 121 amino acids, which is not in SARS-CoV-1, and a similar variation occurs in the 3b protein (33). Therefore, our review will provide clear insights to focus more on the spike protein and entry-level mechanism of SARS-CoV-2 for potent antivirals and vaccines development.

### *Repurposing of SARS-CoV-1 entry-inhibitors other than the tested antivirals for COVID-19*

Repurposing antivirals from amongst viral strains is an intelligent strategy to find out the effective antivirals against contagious novel pandemic strain like SARS-CoV-2. Therefore, our study has mainly attributed the similarities between the SARS-CoV-1 and SARS-CoV-2 as they both share significant similarities, including beta-genus family and extends the similarities in spike protein, entry mechanism and RBD as shown in the Figure. However, the difference exists in few amino acid sequences aligned in spike protein; the domain arrangements of similarity exist to SARS-CoV-1 to SARS-CoV-2. Hence our study also recommends for repurposing the antivirals which were potential to spike protein inhibition against SARS-CoV-1, either *in vitro* or *in silico* evaluation were highlighted in *Table 1* (34-56) as these antivirals were not studied on SARS-CoV-2 so far. *Table 2* recommends a few efficient non target based antivirals against SARS-CoV-1 either through *in vitro* or clinical studies has been highlighted for future trial purpose (57-66). Shanmugaraj *et al.* has summarised the therapeutic measures of potential monoclonal antibody against SARS-CoV-1 and MERS-CoV entry mechanism as a significant target where the current review has focussed on antivirals exclusively (25). Haagmans *et al.* has summarised possible *in vitro* and *in vivo* neutralising monoclonal antibodies, and potential immunotherapy against SARS-CoV-1 entry inhibitors has been updated (67).

## Update on current antiviral therapy on SARS-CoV-2

### *Drug discovery against SARS-CoV-2 by in silico study*

The computational approach to screen the effective antivirals from the available compounds is much desirable, time consuming and more rapid method to screen the potent compound when compared to *in vitro* and *in vivo* evaluation. Within the short period, several research crews have studied the molecular docking with available proteins from the PDB and docked with a compound

 

**Table 1** List of potential antivirals/natural molecules/peptides against spike protein/entry mechanism of SARS-CoV-1

| Antivirals | Mode of action | Method of study | Effective concentration | Reference |
|---|---|---|---|---|
| Tetrandrine (TET), fangchinoline (FAN), and cepharanthine (CEP) | S and N protein | *In vitro* | 295.6, 919.2 and 729.7 nM respectively | (34) |
| Emodin and Chinese medicinal cpds | S protein and ACE2 | *In vitro* | 1 to 10 μg/mL | (35) |
| 12 synthetic peptides and 12 residues | S protein and ACE2 | *In vitro* | 0–20 nmol | (36) |
| Biacalin | Renin and ACE | *In vitro* | 120.36 μM | (37) |
| Saikosaponins (medicinal plant cpd) | Viral attachment | *In vitro* | 6 μM | (38) |
| Tetra-O-galloyl-beta-D-glucose (TGG) (medicinal plant cpd) | Entry inhibitor | *In vitro* | 4.5 μM | (39) |
| Chloroquine and Ammonium chloride | Entry inhibitor | *In vitro* | 100 μM chloroquine and 20–40 μM NH4Cl | (40) |
| MLN-4760 (peptide substrate) | ACE2 | *In silico* | Arg273, His505, and His345 | (41) |
| N-(2-aminoethyl)-1 aziridine-ethanamine | ACE2 | *In vitro* and *in silico* | 57±7 μM and (-23-7 docking score) | (42) |
| Synthetic peptides derived from HR1 and HR2 | Spike protein | *In vitro* | 10 μM | (43) |
| E64d, and ammonium chloride | ACE2 and cathepsin | *In vitro* | 2.5 μg | (44) |
| Amiodarone | Endosomal proteinase cathepsin | *In vitro* | 10 μM | (45) |
| 18 synthetic proteins | Spike and ACE2 | *In vitro* | <10 μM | (46) |
| K26 and D30 (peptides) | Spike and ACE2 | *In vitro* | 50 and 6 μM | (47) |
| Peptide 9626 (S residues 217-234) | ACE2 | *In vitro* | 11 μM | (48) |
| HR1-1 and HR2-18 | Viral fusion | *In vitro* | 0.14 and 1.19 μM | (49) |
| HR1 and HR2 peptides | Protease-mediated cell surface pathway | *In vitro* | 1 nM to 100 μM | (50) |
| Small interfering RNA | Silencing Spike gene | *In vitro* | Significantly reduce viral copy number | (51-55) |
| Griffithsin (GRFT) | Spike protein | *In vitro* and *in vivo* | 48 nM/cytokines were significantly reduced in GRFT-treated animals | (56) |

ligand structure. *Table 3* explicits the efficiently docked chemical compounds to various protein targets of SARS-CoV-2. Many of the docking studies have attempted with the main protease of SARS-CoV-2 using online docking software. There are seven *in silico* studies investigated the binding affinity against SARS-CoV-2 proteins and enzymes (26,31,68-72). Saquinavir (SQV) and lopinavir binding energy with the main protease was higher than HIV and SARS-CoV-1 (69). Wu *et al.* have studied 78 different antivirals on various SARS-CoV-2 protein (26). Remdesivir has exhibited high binding energy on Nsp3b (–36.5), RdRp (–112.8) amino acid residues. Darunavir has docked to NsP3c (–126.149), PLpro (–110.759) as chloroquine has docked to Nsp3b with the binding energy (–130.355) (26). Disappointingly darunavir has not shown any potential activity against SARS-CoV-2 strain through *in vitro* study at the concentration of EC50 >100 μM which was compared with remdesivir as a positive control (73).

### *Drug discovery by in vitro study against SARS-CoV-2*

The effective drug discovery approach by *in vitro* study from the existing drug is the second fastest protocol to identify antivirals against newly emerged viral infections. Wang

 

**Table 2** List of efficacious antivirals identified by clinical trial/*in vitro* study on SRAS-CoV-1 infection

| Antivirals | Method of study | Method of experimentation | Effective concentration | Reference |
|---|---|---|---|---|
| Lopinavir/ritonavir, ribavirin | *In vitro* | Plaque reduction assay | 4 μg/mL, 50 μg/mL | (57) |
| lopinavir/ritonavir | Clinical study | 75 patients | lopinavir 400 mg/ritonavir 100 mg orally every 12 hrs | (58) |
| Ribavirin, fluorquinolone, azithromycin, quinolone, levofloxacin | Clinical trial study | (A) 40 patients with Ribavirin, cefoperazone/sulbactam); (B) 30 with fluoroquinolone, azithromycin, recombinant interferon alpha and restricted steroid use; (C) 60 with quinolone, azithromycin, some given recombinant interferon alpha, steroid use when symptoms worsen; (D) 60 levofloxacin, azithromycin, of which 45were given recombinant interferon alpha | Treatment D has responded well. All patients recovered | (59) |
| Ribavirn, levofloxacin, thypentin, azithromycin | Clinical trial study | 29 patients with ribavirin, levofloxacin, thyopentin, azithromycin, methylprednisolone, 20 patients with treatment: control group treatment + TCM recipes | All patients recovered | (60) |
| IFN-alfacon-1 | Clinical study | 9 patients | All recovered | (61) |
| Ribavirin and corticosteroids | Clinical study | 1,755 patients in Hong Kong and 191 patients in Toronto | Combinational therapy worked well than monotherapy | (62) |
| Convalescent plasma | Clinical study | 40 patients | Patients received convalescent plasma had shorter hospital stay and low mortality | (63) |
| Interferon type I | *In vitro* study | CPE, plaque reduction assay conducted in vero cells | Evidence of some antiviral effect. In comparison to interferon alpha and beta drug, interferon beta is expressing better outcome | (64-66) |

*et al.* have studied multiple drugs including remdesivir, chloroquine (GS5734), ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine and favipiravir against SASR-CoV-2 (74). Among these, remdesivir ($EC_{50}$ =0.77 μM) and chloroquine ($EC_{50}$ =1.13) are identified as a potent inhibitor against SARS-CoV-2 at low molar concentration. Evidently, in time dose-dependent assay chloroquine has shown appreciable inhibitory activity on before and after entry level experimentation. Lopinavir/Ritonavir has a significant role in SARS-CoV-2 and so where tested in 16 patients reported in Wuhan city either independently or in the combination of arbidol (75). The investigation supports that combinational treatment has been more efficacious than lopinavir/ritonavir as monotherapy. As per the Chinese national health guidelines, lopinavir/ritonavir (400 mg/100 mg bid po) and IFN-alpha (5 million U bid inh) are recommended for SARS-CoV-2 treatment (18,76).

HCQ ($EC_{50}$ =0.72 μM) was found more potent against SARS-CoV-2 than chloroquine which exhibited as $EC_{50}$ =5.7 μM in Vero cell line (77). Ivermectin (5 μM) has exhibited potential inhibitory activity against SARS-CoV-2 at 5,000 fold reduction of viral copy number compared to the control and $IC_{50}$ was around approximately 2 μM based on protein target dependence of infected strain (78). Lianhuaqingwen (LH), a compound from the Chinese medicinal plant, was evaluated for its efficacy against SARS-CoV-2 showing an $IC_{50}$ 411.2 μg/mL (LH) by CPE assay and considering remdesivir, as positive control at $IC_{50}$ of 0.651 μM by plaque reduction assay (79). The authors have also studied the immunomodulatory effect of LH and

 

**Table 3** List of antivirals and natural molecules showing their docking efficiency on SARS-CoV-2 (compiled from publications)

| Compounds | SARS-CoV-2 target | Hydrogen bond score | Amino acid residue | Binding energy (K Cal/mol) | Medical indication in drug bank | Reference |
|---|---|---|---|---|---|---|
| 78 antiviral compounds | 19 different targets including 3CLpro, Spike, RdRp, and PLpro | NP | Provided | Provided | Varies | (26) |
| Baicalin | ACE2 receptor | NP | ASN-149, ARG-273, HIS-505 | –8.46 | Chinese Medical plant cpd | (31) |
| Scutellarin | ACE2 receptor | NP | GLU-495, UNK-957, ARG-482 | –14.9 | Chinese Medical plant cpd | (31) |
| Hesperetin | ACE2 receptor | NP | TYR-613, SER-611, ARG-482, GLU-479 | –8.3 | Chinese Medical plant cpd | (31) |
| Nicotianamine | ACE2 receptor | NP | ARG-518, GLU-406, SER-409, GLN-522, GLN-442 | –5.1 | Chinese Medical plant cpd | (31) |
| Glycyrrhizin | ACE2 receptor | NP | ARG-559, GLN-388, ARG-393, ASP-30 | –9 | Chinese Medical plant cpd | (31) |
| Colistin | Main protease | 9 | THR24, THR25, THR26 | NP | Antibiotic | (68) |
| Valrubicin | Main protease | 7 | THR24, THR25, THR26, ASN28, ASN119 | NP | Anthracycline, antitumor | (68) |
| Icatibant | Main protease | 6 | ASN28, ASN119 | NP | Hereditary angioedema | (68) |
| Bepotastine | Main protease | 5 | THR25, THR26, ASN119 | NP | Rhinitis, urticaria/ pruritis | (68) |
| Epirubicin | Main protease | 4 | ASN28, ASN119 | NP | antitumor | (68) |
| Epoprostenol | Main protease | 4 | ASN119 | NP | Vasodilator, platelet aggregation | (68) |
| Vapreotide | Main protease | 3 | THR24, ASN28, ASN119 | NP | Antitumor | (68) |
| Aprepitant | Main protease | 3 | ASN28, ASN119 | NP | Nausea, vomiting, anti-tumour | (68) |
| Caspofungin | Main protease | 3 | ASN119 | NP | Antifungal | (68) |
| Perphenazine | Main protease | 2 | ASN28, ASN119 | NP | Antipsychotic | (68) |
| Saquinavir | Main protease | NP | NP | –9.6 | Antiviral | (69) |
| Lopinavir | Main protease | NP | NP | –9.1 | Antiviral | (69) |
| Tipranavir | Main protease | NP | NP | –8.7 | Antiviral | (69) |
| Darunavir | Main protease | NP | NP | –8.2 | Antiviral | (69) |
| Amprenavir | Main protease | NP | NP | –7.6 | Antiviral | (69) |
| Atazanavir | Main protease | NP | NP | –7.2 | Antiviral | (69) |
| Ritonavir | Main protease | NP | NP | –6.9 | Antiviral | (69) |
| 16 drugs (include FDA approved and non approved drugs) | polyprotein PP1AB and 3CLpro sequence | NP | 86% similarities between two target enzymes for overall drug candidates | –8 to –10.1 | Varies | (70) |
| 38 compounds source-plants | ACE2 receptor and main protease | NP | NP | –7.9 to –19.9 | Chinese respiratory medicinal plants cpd | (71) |
| Theaflavin | RdRp | NP | Arg553 | –8.8 | Chinese Medical plant cpd | (72) |

SARS-CoV-2, severe acute respiratory syndrome-related coronavirus 2; cpd, compounds; NP, not provided; ACE2, angiotensin converting enzyme 2; CLpro, C like proteinase; RdRp, RNA dependent RNA polymerase; PLpro, papain like protease.

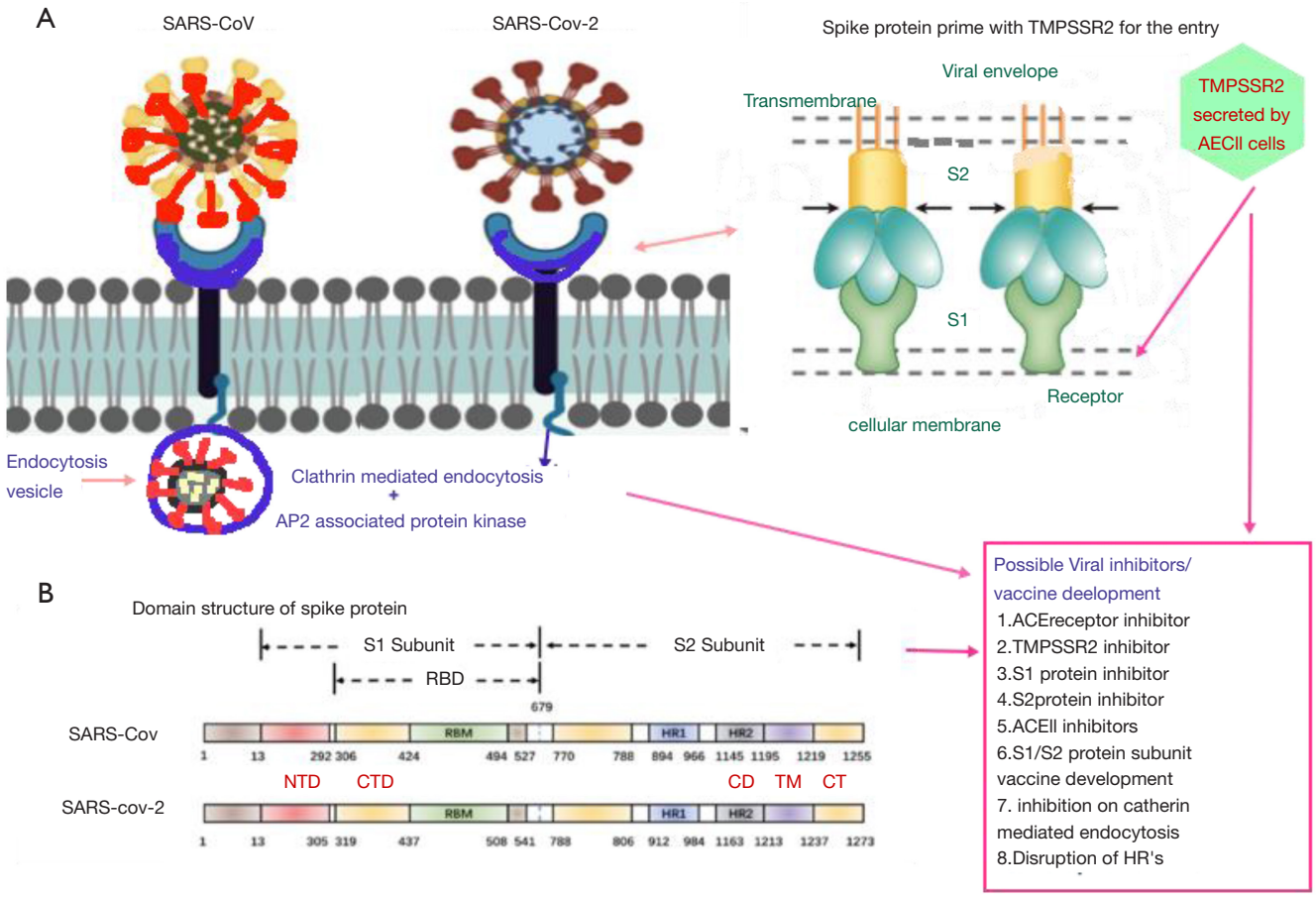


**Figure 1** Schematic representation of similarities between SARS-CoV-2 and SARS-CoV-1 and overview of possible targets for SARS-CoV-2 antiviral prediction. (A) The entry process for both (SARS-CoV-1 and SARS-CoV-2) access the similar mechanism where ACEII is the common receptor and prime with TMPSSR2 and enters into the host cell. Once it enters with the help of spike protein, both cells undergo Clathrin mediated endocytosis with the association of AP2 associated protein kinase. Therefore, the effective antivirals studied for SARS-CoV-1 could be used for SARS-COV-2 for better prediction as it has same mechanism. (B) Domain structure of SARS-CoV-1 and SARS-CoV-2 where S1 and S2 protein. SARS-CoV-2, severe acute respiratory syndrome-related coronavirus 2; RBD, receptor binding domain; RBM, receptor binding motif; HR, heptad repeats; NTD, N terminal domain; CTD, C terminal domain; CD, cytoplasmic domain; TM, transmembrane; CT, cytoplasmic tail.

observed elevated expression of four cytokines (TNF-α, IL-6, CCL-2/MCP-1, and CXCL-10/IP-10) with a significant difference. The antiviral activity of ribonucleoside analogue ßd-N4-hydroxycytidine (NHC) (EIDD-1931) was studied against SARS-CoV-2, SARS-CoV-1 and MERS-CoV in Vero cells and Calu-3 cells (80). The effective inhibitory concentration was $IC_{50}$ of 0.3 µM and $CC_{50}$ of >10 µM in Vero cells and 0.08 µM in Calu-3 cells.

Hoffmann *et al.* stated that the spike protein shares about 76% amino acid identity with SARS-CoV-1 (81) and studied the mechanism of entry through ACE receptor to the host cell. The research crew has performed *in vitro* study and demonstrated the cellular serine protease, TMPRSS2 priming with SARS-CoV-2 for the entry. The study demonstrated the Camostat mesylate as TMPRSS2 inhibitor which blocks the activity of CatB/L and TMPRSS2 priming and thereby inhibits entry of SARS-CoV-2 virus into host cell (81). Teicoplanin has shown a better antiviral efficiency on SARS-CoV-2 at 1.66 µM 50% inhibitory concentration against targeting cathepsin

 

L protein which is used for cell entry where vancomycin and other test antibiotics did not exhibit any appreciable inhibitory activity against Cathepsin L protein (82).

### *Highlights from clinicians for medications against COVID-19 through publications*

A case report on US first patient's medications history could help other clinical practice to treat baseline respiratory syndrome symptoms (83). Once after the confirmation of positive PCR test results, the patient had been treated according to his/her symptoms existed. Apart from the antipyretic and hospital-acquired pneumonia treatment, the patient had treated with remdesivir and provided with oxygen supply (83). Zhang *et al.* have mentioned oral moxifloxacin or levofloxacin (consider tolerance) and arbidol for COVID-19 bacterial co-infection treatment (20). The emergency cases, were treated with antiviral plus anti-pneumococcus plus anti*Staphylococcus aureus* with nemonoxacin (750 mg once daily) and linezolid (20). SpO2 <90%, dexamethasone 5–10 mg or methylprednisolone 40–80 mg was given intravenously for emergency cases. Oral oseltamivir was widely used in china hospitals for the treatment for COVID-19 cases which is considered as neuraminidase inhibitors (76). Corticosteroids are not recommended for COVID-19 disease where it has shown numerous side effects such as septic shock, myocardial lung injury and similar symptoms of acute respiratory syndrome disease (84). However, based on the china government guidelines, some clinicians are recommending corticosteroids in a mild dose (≤0.5–1 mg/kg per day methylprednisolone or equivalent) for ≤7 days to treat critical cases (85).

The synergistic effect of the combinational treatment of HCQ (600 mg/d for 10 days) and azithromycin (500 mg day 1 and 250 mg days 2 to 5) has treated for 36 COVID-19 patients based on the PCR confirmation. Among the selected cohorts, 26 patients had received HCQ and 10 were in the control group (86). Among these 26, six patients have showed 100% cure who has administered with HCQ and azithromycin whereas drug HCQ alone has shown 57% cure from COVID-19 disease. Perhaps, none of the patients has received azithromycin alone. Hence it would be appreciated to call it combinational efficacy than its synergistic efficacy. Similarly, the synergistic effect has reported by the same clinical team from France in 80 clinically ill patients (includes six patients published in previous publication) on the potential treatment of HCQ and azithromycin (87). All patients have responded well with the synergistic treatment except two non-responders. However, the disagreement on using of HCQ and Azithromycin combination has been raised in the study which is the highlights to be considered. The prospective study has administered HCQ (600 mg/d for 10 days) and azithromycin (500 mg day 1 and 250 mg days 2 to 5) conducted in 11 consecutive patients. The results were still observed the positive viral load even on 6$^{th}$ day after the combinational treatment initiation (88).

The monotherapy of HCQ have demonstrated effective and appreciable results in few studies which should be noted. In a prospective study, 30 patients have received 400 mg of HCQ per day for five consecutive days plus conventional treatments and were compared with a group who received only conventional treatment (89). On day 7, the effect of HCQ was observed in 13 (86.7%) cases where the control group had observed 14 (93.3%) cases on evidence as negative in throat swabs. The effect of HCQ was almost equal and effective as conventional treatment, and hence authors suggested to study with a large cohort to investigate the effect of HCQ in COVID19 patients (89). Yao *et al.* have suggested HCQ (400 mg) can be given twice daily/day and gradually 200 mg of HCQ twice daily for four more days as a maintenance dose for the COVID19 treatment (77). The research crew has stated HCQ (EC50 =0.72 μM) was efficient against SARS-CoV-2, than chloroquine (EC50 =5.47 μM) and also studied the plasma/blood profile through pharmacokinetics by *in silico* methods. Comparatively blood and plasma concentration of HCQ have been increased rapidly and maintained steady stability (77). Though the drug remdesivir has demonstrated side effects in 102 (66%) of 155 remdesivir recipients, it was reported as an effective therapeutic agent on developing appreciable clinical improvement when compared to placebo (90).

## Immunotherapy

Antibody therapy and immunotherapy is another genre of therapeutic measures. The following segment summarises the published domains attempt for any invention. The possible cross-protection of SARS-CoV-1 RBD against SARS-CoV-2 can be a potential target as earlier results of anti-SARS vaccines have cross neutralise other Bat-originated SARS strains (91). SARS-CoV-1 potent neutralising antibodies m396, CR3014, CR3022 were tested for the efficacy on comparing with irrelevant anti-

 

CD40 as control. The anti-SARS-CoV-1 RBD neutralising mAbs 80R and S230 were studied for the docking affinity to SARS-CoV-2 proteins by virtual screening (92). Among these CR3022 showed better affinity towards ACE2 binding site of SARS-CoV-2 while the other two antibodies failed to bind with SARS-CoV-2 spike protein (30). Based on the study results, CR3022, could be considered as significant therapeutic measures or vaccine candidates for COVID-19 disease. Grifoni *et al.* have studied the SARS-CoV-1 B cell and T cell epitope mapped with SARS-CoV-2; herein demonstrated that they both have an average 60–90% similarity (28). Recently convalescent plasma therapy is a classic adaptive immunotherapy to consider ailments for many diseases. Likewise, plasma therapy is contributing its importance as a promising treatment option to COVID-19 disease indeed. Clinicians has treated on 10 severe patients with one dose of 200 mL of convalescent Plasma transfusion with neutralising antibody titre 1:640 and observed massive development in median time 16.5 days where there were no any severe adverse effects which is noticeable (93). Passive immunisation is the best effective prophylaxis of any viral infection. Convalescent plasma (IgG) with a binding titre greater than 1:1,000 dilution was transfused to five critically ill patients and observed better improvement in all the patients (94).

## Update on antivirals registered for clinical trials

As of April 11, a total of 51 recruited clinical trials has been started aiming to evaluate the efficacy of antiviral for the treatment of COVID-19 infections all over the world, as recorded in NIH, US library of Medicine (https://clinicaltrials.gov/ct2/home) is tabulated (*Table 4*). Indian clinical trials committee has launched clinical trials on HCQ against SARS-CoV-2 (CTRI/2020/03/024402) (*Table 4*). China has launched 303 ongoing clinical trials, among them, 16.5% (50 trials) has attempting with compounds from traditional Chinese Medicine and 4.6% (14 trials) were analysed for the combined effect of TCM with Western Medicine (10). The Chinese clinical trials are available on Chinese clinical trial registry (http://www.chictr.org.cn/abouten.aspx).

## Strategies on vaccines development for SARS-CoV-2

The S protein plays a significant role in neutralising antibody, T cell response and defensive immunity developed by their viruses during the infection (95). There are different types of target available for vaccines development such as full-length S protein, DNA-based, Viral vector, recombinant S protein-based, RBD, DNA-based, viral vector-based, Recombinant RBD protein-based development. Each of the mentioned vaccine candidate has their advantage and disadvantages on respective strategy (95). Only a small number of vaccine development has attempted for SARS-CoV-1 which had reached clinical trials. WHO reports about 120 projects from many pharmaceutical companies and universities on the development of a vaccines have been registered all over the world (96). Among that, six had been approved for clinical trials for evaluation.

The American company, Moderna has registered for phase I clinical trial on mRNA vaccine development (phase 1 clinical trial NCT04283461). Innovio has started on DNA vaccine development with 40 volunteers (phase 1 NCT04336410) started at the beginning of April. The University of Queensland had started to work on the virus in cell cultures which are at preclinical testing (which are hopefully started at early April). The University of Oxford in England has started recombinant vaccine trials in 500 volunteers (phase 1/2 NCT04324606). Johnson and Johnson and Sanofi are joining hands for the vaccine development to SARS-CoV-2 with 200 volunteers. Inactivated candidate vaccine has been approved from the developer Sinovac and Beijing Institute of Biological Products/Wuhan Institute of Biological Products starting from April (phase 2 ChiCTR2000031781 and phase 1 ChiCTR2000030906). Meanwhile, some vaccines development crew from Netherland and Australia are aiming to conduct clinical trials on the use of tuberculosis vaccine to SARS-CoV-2.

## Summary and perspectives

The rapid pandemic swept of COVID-19 disease across China, and the world made it as a global health crisis recently. Since the elderly and medically critically ill patients are more susceptible, it requires effective instant antivirals to be identified as soon as possible. The pharmaceutical industry and clinical trials are working to develop antivirals to combat COVID-19 disease. Thanks to research crews for characterisation of viral life cycle and studies on viral characteristics within the short period that could be able to bring out the similarities and dissimilarities with SARS-CoV-1 that predict several hosts and viral

 

**Table 4** List of antivirals clinically tried for COVID-19 and their efficacy status

| Clinical trial number | Antiviral/compounds | Study type | Phase | No. of patients | Country |
|---|---|---|---|---|---|
| NCT04333550 | Deferoxamine | Interventional | I and II | 50 | Iran |
| NCT04328272 | Hydroxychloroquine and azithromycin | Single centred single-blind RCT | III | 75 | Pakistan |
| NCT04333407 | Aspirin, clopidogrel, rivaroxaban, atorvastatin, omeprazole | Interventional | NA | 3,170 | UK |
| NCT04335123 | Losartan | Interventional | I | 50 | US |
| NCT04329832 | Hydroxychloroquine *vs.* azithromycin | Interventional | II | 300 | US |
| NCT04317092 | Tocilizumab | Interventional | II | 400 | Italy |
| NCT04304053 | Darunavir and hydroxychloroquine | Interventional | III | 3,040 | Spain |
| NCT04334382 | Hydroxychloroquine *vs.* azithromycin | Interventional | III | 1,550 | US |
| NCT04333225 | Hydroxychloroquine | Interventional | II | 360 | US |
| NCT04307693 | Lopinavir/ritonavir or hydroxychloroquine | Interventional | II | 150 | Korea |
| NCT04331834 | Hydroxychloroquine | Interventional: RCT | III | 440 | Spain |
| NCT04292899 | Remdesivir | Interventional | III | 2,400 | US |
| NCT04332094 | Hydroxychloroquine, azithromycin, and tocilizumab | Randomized | II | 276 | Spain |
| NCT04292730 | Remdesivir | Randomized | III | 600 | US |
| NCT04325061 | Dexamethasone | Randomized | IV | 200 | Spain |
| NCT04331795 | Tocilizumab | Non-randomized | II | 50 | US |
| NCT04305106 | Bevacizumab | Randomized | NA | 140 | China |
| NCT04320615 | Tocilizumab | Randomized | III | 330 | US |
| NCT04280588 | Fingolimod | Non-randomized | II | 30 | China |
| NCT04337359 | Ruxolitinib | Expanded access | NP | NP | Switzerland |
| NCT04326725 | Hydroxychloroquine plus vitamins-zinc | Observational | | 80 | Turkey |
| NCT04273321 | Corticosteroids | Randomized | NA | 400 | China |
| NCT04333914 | Chloroquine, nivolumab, tocilizumab | Randomized | II | 273 | France |
| NCT04328012 | Lopinavir/ritonavir, hydroxychloroquine sulfate, losartan | Randomized | II and III | 4,000 | US |
| NCT04255017 | Abidol hydrochloride, oseltamivir, lopinavir/ritonavir | Randomized | IV | 400 | China |
| NCT04254874 | Abidol hydrochloride combined with interferon atomization | Randomized | IV | 100 | China |
| NCT04323761 | Remdesivir | Expanded access | NP | NP | US |
| NCT04261270 | Ritonavir + oseltamivir, ritonavir + oseltamivi, oseltamivir | Randomized, open, controlled | III | 60 | China |
| NCT04310228 | Favipiravir combined with tocilizumab | Randomized | NA | 150 | China |
| NCT04332991 | Hydroxychloroquine | Randomized | III | 510 | US |
| NCT04320238 | Recombinant human interferon alpha-1b and thymosin alpha 1 | Non-randomized | III | 2,944 | China |

**Table 4** (*continued*)

 

**Table 4** (*continued*)

| Clinical trial number | Antiviral/compounds | Study type | Phase | No. of patients | Country |
|---|---|---|---|---|---|
| NCT04315948 | Remdesivir, lopinavir/ritonavir, interferon beta-1a, hydroxychloroquine | Randomized | III | 3,100 | France |
| NCT04275414 | Bevacizumab | Single group assignment | II and III | 20 | China |
| NCT04291729 | Ganovo + ritonavir +/– interferon nebulization | Single group assignment | IV | 11 | China |
| NCT04305457 | Nitric oxide | Randomized | II | 240 | US |
| NCT04320277 | Baricitinib | Non-randomized | III | 60 | Italy |
| NCT04257656 | Remdesivir | Randomized | III | 453 | China |
| NCT04322344 | Escin | Non-Randomized | II and III | 120 | Italy |
| NCT04333654 | Hydroxychloroquine | Randomized | I | 210 | US |
| NCT04325893 | Hydroxychloroquine | Randomized | III | 1,300 | France |
| NCT04322396 | Azithromycin and chloroquine | Randomized | II | 226 | Denmark |
| NCT04324073 | Sarilumab | Randomized | II and III | 240 | France |
| NCT04322773 | Tocilizumab, sarilumab | Randomized | II | 200 | Denmark |
| NCT04340557 | Losartan | Randomized | IV | 200 | US |
| NCT04322123 | Hydroxychloroquine | Randomized | III | 630 | Brazil |
| NCT04323527 | Chloroquine | Randomized | II | 440 | Brazil |
| NCT04322682 | Colchicine | Randomized | III | 6,000 | US and Canada |
| NCT04261517 | Hydroxychloroquine | Randomized | III | 30 | China |
| NCT04275245 | Meplazumab | Single group assignment | I and II | 20 | China |
| NCT04280224 | NK cells | | I | 30 | China |
| NCT04244591 | Methylprednisolone therapy | Randomized | II and III | 80 | China |
| CTRI/2020/03/024402 | Hydroxy chloroquine | Randomized | III | 500 | India |

proteins targeting molecules to provide the promising antiviral candidates. We have examined published evidence in support of the similarities between SARS-CoV-2 and SARS-CoV-1 in entry-level mechanism and spike protein alignment that enable us to predict the effective antivirals. Owing to the major appreciable similarities in structure and clinical manifestation, leaving aside high R°, the most efficacious drug on SARS-CoV-1 infection could be tried as antivirals to treat COVID19. Also, the expertise and potent highly immunogenic/antiviral component identified for SARS-CoV-1 would be consider for repurposing against spike-based or entry-based target to inhibit SARS-CoV-2 replication. Our review might galvanize the current research and professional community to evolve with significant findings to treat COVID-19 disease.

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