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Investigational Anti SARS-COVID 19 Medication

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Abstract. The newly identified severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that originated in December 2019 in Wuhan, China. By July 2020, the WHO reported over 17 million confirmed cases in over 200 countries around the globe. This review discusses how the COVID-19 pandemic may affect healthy people, structure and replication cycle of SARS-CoV-2; targets and therapeutics SARS- CoV-2 and anti-COVID drugs: strategies and perspectives.

Keywords: SARS-CoV-2, structure and replication, therapeutics drugs, multidrug combination, transmission of SARS-CoV-2

1 Introduction

The SARS-CoV-2 pandemic, declared as a global health emergency by the WHO in February 2020, has currently infected more than 17 million people with fatalities near 700,000 and increasing exponentially, in absence of vaccines and drugs. In this review, we focus on potential drug gable targets and suitable therapeutics, currently being explored in clinical trials, to treat SARS-CoV-2 infection.

The coronavirus disease 2019 (COVID-19) is a global pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that has posed serious threats to humans. The SARS-CoV-2 infection emerged in December 2019. Soon, it spread across the globe causing a pandemic and has become a major health concern [1, 2]. As of 1st June 2020, the WHO reported a total of 17,057,853 cases world wide with 690,166 deaths due to COVID-19 [3].

Coronaviruses belong to the Coronoviridae family, consisting of four genera, namely Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus.

The SARS-CoV-2 belongs to the Betacoronavirus genera [4]. Like all coronaviruses, SARS-CoV-2 is a positive stranded, non-segmented RNA virus. It is shown that coronaviruses have the largest genome among all of RNA viruses, ranging from 27–32 kD [5]. Clinical features of SARS-CoV-2 infection are similar to SARS and MERS. Clinical symptoms of SARSCoV-2 infection include fever, fatigue, dry

cough and dyspnea, which may progress into acute respiratory distress syndrome (ARDS) causing death [5]. SARS-CoV-2 is highly contagious and has exhibited transmission through fomites, cough and cold droplets and human contact [2].

1.1 Structure & replication cycle of SARS-CoV-2

The SARS-CoV-2 has a spherical and pleomorphic form [7]. SARS-CoV-2 has a single-stranded, nonsegmented, positive sense RNA. Most of the genomic material is constitute by replicase gene, which codes for 16 nonstructural proteins (nSPs). The rest of the genome codes for structural proteins (SPs) of the virus [2, 16].

The structural proteins of SARS-CoV-2 are: a) spike glycoprotein (S), b) nucleocapsid proteins (N), c) membrane proteins (M) and d) envelope proteins (E) [6, 8, 9, 16]. The spikes are seen as protrusions from the virus surface, giving the appearance of a crown to the virus (fig.1).

The S proteins are glycoproteins, which help SARS-CoV-2 to attached and penetrate of the virus into the host cell [6].

The S protein is made by 2 subunits – which are called S1 and S2. The main function of S1 is to bind for the host cell receptor; S2 is involved in fusion of the viral and cell membranes [11]. The S protein has to be primed for activation and entry of the SARS-CoV-2 into the host cell [12, 13, 14, 15].

The RNA genome of SARS-CoV-2 is packaged inside of capsid, the capsid is formed by the N proteins, surrounded by a phospholipid bilayer envelope [6, 16]. The M and E proteins are embedded in the viral envelope and are involved in post RNA translation of SARS-CoV-2. The function of M proteins is to interact with other structural proteins, and in this form aid formation of envelope and bud release [2, 6, 16]. E proteins play pivotal role in ion channels and are also involved in the assembly of the virus during replication [16].

1.2 Replication cycle of SARS-CoV-2

The replication cycle of SARS-CoV-2 is divided into three processes – first is viral entry, second RNA replication, assembly and third exit from the host cell.

It is suppose that some host cell proteins will be associate with S protein of SARS-CoV-2, and in this way facilitating viral invasion into cells. It was reported that SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as a receptor for entry into the host cell, similar to SARS-CoV [11, 13, 15, 17].

Also recent studies from different research group show two other receptors which are involved; GRP78 and CD147. CD147, is placed in surface of a transmembrane glycoprotein of the host cell and has been proposed as an alternative pathway for infection [18, 19, 20]. Publication from this authors predicted the binding of S protein to GRP78; a chaperone heat shock protein in cells.

It is shown that receptor binding domain (RBD) of S1 subunit binds to ACE2 on the cell surface. To inactivate S protein it is necessary to cleaved at the S1/S2 and S2' sites for further viral entry into the host cell. Other studies on the coronavirus S proteins have reported many host proteases which are involved in the spike activation like TMPRSS2, cathepsin L, B, furin and trypsin; this is shown by many authors [9, 14, 15]. Depending on their availability, the mechanism of viral entry differs;

previous reports have recorded entry of SARS-CoV either via an endocytic pathway or direct fusion with plasma membrane.

Many authors report that surface proteases of the host cells like TMPRSS2 (exogenous trypsin) can cleave the S protein, and in this way triggering fusion of viral and plasma membranes, facilitating direct release of the viral genome into the cytoplasm. The same authors report that SARS-CoV can also enter the cell by endocytosis. Endosomal cathepsin B and L cleave the S protein, and in this form resulting in fusion of the viral and endosomal membranes and subsequent release of viral genome [9, 13, 14, 15, 21, 22].

Once the virus enters the host cell, it releases the RNA genome into the cytoplasm. The gene called replicase on the positive sense of RNA is directly translated to a polyprotein, pp1ab. After that the polyprotein pp1ab after that is cleaved by viral proteases; 3-chymotrypsin like protease (3-CL pro) and papain like protease (PL-pro) to form 16 individual nSPs [23]. In another side nSPs, on assembly, form the RNA replicase-transcriptase complex (RTC). The RTC is localized in the double membrane vesicle (DMV) near the ER [9]. It is shown that RTC is involved in replicating and transcribing the RNA genome into a set of negative sense RNAs. Full-length of negative sense of RNAs act as templates for transcribing the genomic RNA. Discontinuously replication by RTC forms partial, negative sense, subgenomic RNA strands. These act as templates for transcription of subgenomic mRNA which code structural proteins (SPs) of the virus [2, 9, 16, 24, 25, 26]. After that mRNA is translated using the cellular ribosomes and in this form are produced the M, N, E, S proteins. Than the SPs are inserted into the ER, from where they are transported to the ER-Golgi Intermediate Complex (ERGIC). In another way the N protein enclosing the genomic RNA with other SPs in ERGIC, and forming viral buds. In the end the mature virions are transported to the cell membrane in a vesicle and in this form they exit the host by exocytosis [2, 16, 9, 24, 25].

1.3 Targets & therapeutics SARS-CoV-2

As we said before the SARS-CoV-2 contains a single-stranded, RNA genome, the largest RNA virus identified till today, which is very similar to the virus that causes SARS and MERS. COVID-19 belongs to the β-coronavirus genus and after sequencing it is shown that 88% sequence homology with bat-SL-CoVZC45 and bat-SL-CoVZC21, and 50% sequence has homology with MERSCoV [27, 28].

This sequencing give us possibilities to show construction of genome of SARS COVID-2. The genome of SARS-CoV-2 is constructed at least by ten open reading frames (ORFs). The first ORF (ORF1ab), encodes 1–16 NSP at the consensus cleavage site. Other ORFs, encode four major structural proteins, such as spike (S), envelope (E), nucleocapsid (N), membrane (M) proteins and several other proteins with unknown functions. As it discussed before the SARS-CoV-2 replication cycle mainly includes virus entry, genome replication, assembly and germination of virions. Interruption of any of this stages of replication are a potential strategy for the development of antiviral agents (Figure 2).

1.4 Anti-COVID drugs: strategies and perspectives

Till today there are currently no effective drugs targeting SARS-CoV-2. Topical methods used to control novel viral diseases is repurposing existing drugs or designing totally new entitled.

Apart from antiviral drugs, in the search area are also drugs from other groups, for example cardiovascular, antibacterial, antimalarial, antiparasitic agents.

For example oleanolic acid are (Triterpene derivatives) agents with confirmed antiviral properties, also effective against SARS-CoV-2. Triterpene compounds, as the basic skeleton, equipped with additional elements of known antiviral (and similar) drugs are currently undergoing intensive studies to determine their suitability for repurposing in COVID-19 therapy.

Till today favipiravir, remdesivir, galidesivir and tilorone as an antiviral drugs have been proposed for introduction into the oleanolic acid structure in C-3 position of the triterpene backbone by the hydroxyimino-, acetate- or dimethylsuccinate group as the linker.

Alkylamine substituent (derived from the chloroquine molecule or its analogs) have been proposed also for attachment via an amide bond at the C-28 position of the triterpene backbone.

A combination of the above-mentioned three elements results in 18 designed complex structures with significant antiviral properties which offering the greatest prospects for use in COVID-19 therapy.

Based on the selected methods of computational chemistry the molecular parameters and the preliminary activity characterizing designed molecules as potential drugs were calculated and predicted.

The results of the above analysis show that among the designed complex structures with potential antiviral activity targeting mainly SARS-CoV-2, the highest therapeutic potential is noted for the compounds containing a molecule of favipiravir in addition to the *N*-alkylaminoalkylamide fragment connected with oleanolic acid.

Owing to the presence of fragments of three drug substances with significant antiviral properties incorporated into one molecule, the molecule will be active in at least two different phases of the coronavirus life cycle as a multitarged drugs [29].

1.5 Clinical trials of repositioning antiviral drugs for COVID-19

Quick transmission of corona virus could be catastrophic for the life; developing new anti-SARSCoV-2 drugs from scratch is impractical to face the pressing global challenge [30]. Drug developing for treatment of SARSCoV-2 is an emerging strategy, because these drugs have known pharmacokinetic and pharmacodynamic properties, side effects and drug regimens [31].

Some scientist suggest to use anti-SARS-CoV, anti-MERS-CoV agents were chosen as an antiviral drug for COVID-19. Furthermore, some known antiviral drugs like nucleoside analogs and protease inhibitors were chosen as a repositioning drug for COVID-19. Some drugs including favipiravir, remdesivir, lopinavir/ritonavir, chloroquine, hydroxychloroquine, ribavirin, darunavir, arb.i.d.ol, were clinically tested against COVID-19 infection which are present in Figure 5. And they are recommended in guidelines of different countries (Table 1) also[32].

1.5.1 Favipiravir

Drug favipiravir was developed by Toyama Chemical (Division of Fujifilm, Tokyo, Japan). After oral administration, favipiravir is converted into the biologically active nucleoside triphosphate form. It was approved for marketing in Japan in March 2014; generally is used as an antiviral treatment for influenza A and B. Many studies have shown that favipiravir has a specific inhibitory effect on SARS-CoV2 (half maximal effective concentration [EC50] = 61.88 μM, 50% Cytotoxic concentration [CC50] >400 μM, and selectivity index [SI] >6.46) [33]. Avipiravir is recommended for use in further research in vivo.

After controlled study (ChiCTR2000029600) enrolled 80 patients, with 35 in the favipiravir group and 45 in the control group [34]. The results showed that the median time for the negative conversion of viral nucleic acids in the favipiravir group was significantly shorter than it was in the participants in the control group (4 vs 11 days; $p < 0.001$). In terms of chest imaging, the rate of improvement was also significantly higher in the favipiravir group than that in the control group (91.43 vs 62.22%; $p = 0.004$).

1.5.2 Remdesivir

The drug remdesivir is a prodrug developed by Gilead Science, whose structure resembles adenosine. Holshue et al. 2020 [35] reported that the first patient with SARS-CoV-2 was treated with intravenous remdesivir, which improved the clinical symptoms, including a decrease in body temperature, no need for oxygen inhalation support and the return of oxygen saturation to 94–96%.

Gilead Sciences Inc., 2020 published the first clinical result from use of remdesivir [36]. In total from 53 patients with COVID-19, it is shown in 36 patients (68%) showed clinical improvement, and 25 patients (47%) were discharged; eight patients (15%) showed worsening and seven patients (13%) died. In 32 patients (60%) it is shown side effects; 12 patients experienced serious side effects.

On 1 May 2020, Gilead Sciences Inc., announced that the US FDA had granted emergency use authorization (EUA) for the investigational antiviral remdesivir to treat COVID-19, and on 8 May 2020, Japan approved remdesivir for use of treatment of patients with COVID-19 [37].

1.5.3 Lopinavir/ritonavir

Third drug lopinavir/ritonavir is recommended as a second-line treatment of HIV. Lopinavir/ritonavir has been proved to be effective in SARS and MERS in vitro and in vivo [63].

Recent evidence suggests that lopinavir has antiviral activity in treatment of SARS-CoV-2 in vitro with an IC50 value of 9.12 μM [64].

Lopinavir/ritonavir was not associated with benefit in hospitalized patients with COVID-19. The difference in mortality between patients treated with lopinavir/ritonavir and the control group failed to reach the statistically significant (19.2 vs 25.0%; difference: -5.8 percentage points; 95% CI, -17.3 to 5.7) [65].

1.5.4 Chloroquine

Chloroquine phosphate has been recommended as an antimalarial drug for more than 70 years. The in vitro anti-SARS-CoV-2 activity of chloroquine phosphate has been identified with an IC50 value of 1.13 μM; in this amount it is shown to be effective in preventing replication of this virus [76]. Gao et.al. 2020 [66] report that chloroquine phosphate was helpful in preventing the progression of COVID-19. In total, 120 patients with SARS-CoV-2 pneumonia were treated with chloroquine phosphate and 110 patients had undetectable viral RNA on the throat swab after the treatment, and 81 patients were discharged. Also it is not shown serious adverse reactions during the treatment with chloroquine. Based on these results, chloroquine phosphate was included in China's 'Diagnosis and Treatment Protocol for COVID-19 (trial version 7)' followed by inclusion into the protocols of several other countries.

1.5.5 Hydroxychloroquine

Hydroxychloroquine had earned a reputation for potential promising role in COVID-19 [38]. Recently, chloroquine and hydroxychloroquine were demonstrated to inhibit SARS-CoV-2 *in vitro* (EC50 = 5.47%μM, EC50 = 0.72%μM, respectively) [39, 67].

The underlying mechanisms were inferred as follows: (1) as weakly alkaline, chloroquine could increase endosomal pH therefore block virus infection [33, 38]; (2) as spike (S) protein angiotensin-converting enzyme 2 (ACE2) blocker. It is shown that chloroquine and hydroxychloroquine interfered with the glycosylation of cellular SARS-CoV receptor thus inhibit virus attacking [40]; (3) as immunomodulant, chloroquine and hydroxychloroquine could counteract pro-inflammatory cytokine storm in critically ill patients with COVID-19 [42, 48].

Unfortunately, the outcomes of hydroxychloroquine in COVID-19 patients were inconsistent in SARS-CoV-2 viral eradication. Gautret et al [39] reported that hydroxychloroquine alone or combined with azithromycin observed better ability of SARS-CoV-2 eradication. At day six post-treatment, 100% of patients treated with combination of hydroxychloroquine and azithromycin had been virologically cured compared to 57.1% in patients treated with hydroxychloroquine alone and 12.5% in control group.

1.5.6 Ribavirin

The most extensively used therapies were ribavirin and ribavirinbased combinations. Ribavirin was reported to tightly bind to SARSCoV- 2 ribonucleic acid (RNA) dependent RNA Polymerase (RdRp) with binding energy of -7.8 kcal/mol, and thus may be used to against COVID-19 [50]. There were 9 studies reporting SARS and MERS patients treated with ribavirin or combinations with ribavirin. The meta-analysis yielded inconsistent results for mortality with RR of between 0.38 and 0.82, while the combination of ribavirin and corticosteroids showed remarkable lower mortality compared with control group.

1.5.7 Tocilizumab

Another drug which is use for patient's treatments with SARS COVI-19 is Tocilizumab. A retrospective, observational study (n = 21) administered 400 mg tocilizumab, an interleukin (IL)-6 blocker, intravenously once to patients who had respiratory failure, shock or organ failure [57]. Although three patients received a subsequent dose, the benefit is unknown (COVID-19 Investigation Team, 2020). However, the potential benefit in decreasing mortality was evident as no deaths were reported out of 21 patients [53].

1.5.8 Ciclesonide

Ciclesonide is another drug which is used for patients with SARS COVID-19. An inhaled corticosteroid for the treatment of asthma, which has been a potential candidate for repurposing in the treatment of patients with MERS or COVID-19 [61]. The dosage used in a current trial was 320 mcg q12h for 14 days [58, 60, 62]. Ironically, systemic corticosteroids are contraindicated in severe pneumonia caused by viruses such as MERS-CoV and SARS-CoV because they suppress the innate immune system, resulting in increased viral replication.

1.5.9 Niclosamide

Another medication undergoing repurposing investigations for SARS-CoV-2 is niclosamide, an oral anthelmintic drug used worldwide at a single dose of 2 g/d. Niclosamide exerts anti-MERS activity, inhibits SARS-CoV replication and abolishes viral antigen synthesis in vitro, [27, 51] and is considered a possible treatment option. However, it is cytotoxic and has low absorption including low oral bioavailability (10%) and although efforts have been made to formulate derivatives to overcome these obstacles, its extensive clinical development as an antiviral agent may still be hindered. An interventional trial has been registered to evaluate the use of chloroquine with or without azithromycin, faviprevir, nitazoxanide or ivermectin for the treatment of patients with COVID-19 in a real-life setting, but recruitment has not commenced as of 14 April 2020 [62].

1.5.10 High-dose intravenous immunoglobulin (IVIG)

The co-administration of high-dose intravenous immunoglobulin (IVIG) at 25 g/d for 5 days (body weight, 66 kg) with moxifloxacin was reported in a case series study [65]. Although no trials are currently recruiting, the IVIG doses used in protocols are in the range of 0.2-0.5 g kg^{-1} day^{-1} and the use of this agent is expected to be limited to patients in severe or critical conditions [62].

2. Multidrug combinations

The combination of multiple drugs is an important strategy for cure SARS-CoV-2 (Table 2). It is common to combine drugs which interfere at different steps of the

virus replication cycle to improve antiviral efficacy and reduce of drug resistance. For example, the combination of endocytosis inhibitors and protein kinase inhibitors blocks viral invasion. Cohen et al. 2020 [69], suggest combination of remdesivir and dendritic protein monoclonal antibodies as an ideal treatment for SARS-CoV-2 infection. Many clinical treatment of patients with SARS-CoV-2 have been carried out, including those with an RDRP inhibitor, such as favipiravir in tablet form, combined with endocytosis inhibitor chloroquine phosphate, in the treatment of COVID-19 (ChiCTR2000030987).

The combination of ribavirin with different types of interferon to enhance the innate antiviral response was the most commonly used in the treatment of patients with a coronavirus infection (such as SARS and MERS) [70, 71, 72].

Another combination is suggested to use such as interferon-β and antiviral drugs, (lopinavir/ritonavir), has also been recommended by clinical experts [73].

3. COVID -19 and Symptoms in different organs

3.1 COVID-19 & digestive symptoms

Further studies have identified the potential transmission of SARS-CoV-2 through blood and feces samples of COVID-19 patients. The SARS-CoV-2 RNA has been detected in anal or rectal swabs and blood of hospitalized COVID-9 patients [74, 78, 81]. In the study by Zhang et al 15 [78] patients tested, eight were oral swabs positive (53.3%), four were anal swabs positive (26.7%), and six blood positive (40%) and three serum positive (20%). Notably, anal swabs were found more test positive than oral swabs; suggesting the transmission of fecal–oral of SARS-CoV-2. Further, in study by Xu et al., 2020 [75] in a clinical investigation of ten pediatric COVID-19 confirmed cases, rectal swabs of eight children (80%) were persistently tested RNA positive even after nasopharyngeal test was negative, presenting the evidence of viral shedding through the GI tract.

3.2 Coronaviral hepatic pathogenesis

SARS-CoV-2 has been linked to mild-to-moderate liver injury; revealed by elevated serum aminotransferases (ALT/AST), bilirubin, hypoproteinemia and prothrombin time prolongation, supported by liver histopathology [77, 79, 81, 99, 101]. SARS-CoV-2 might directly affect intrahepatic bile ducts this is shown by single-cell RNA sequencing data from two distinct cohorts of COVID-19 patients when it is shown elevated expression of Angiotensin Converting Enzyme-2 receptor in cholangiocytes (59.7%) than hepatocytes (2.6%) [80]. In a recent clinical study of 194 COVID-19 patients, 30 patients (15.46%) showed liver dysfunction [81].

Chronic liver disease patients with impaired immunity because of classical hepatitis viruses (HBV, HCV, HDV and HEV) or other hepatotropic viruses (HGV, GBV, TTV and SENV) infection or nonalcoholic fatty liver disease/nonalcoholic steatohepatitis are more susceptible to COVID-19 [82].

SARS-CoV-2 is also proposed to cause viral hepatitis while inducing a dysregulated innate immune response [83].

In the study by Wen et al., 2020 [84] it is shown the level of CD4+ and CD8+T were decreased significantly, inflammatory genes were highly expressed in these patients. The B plasma cells were found to be increased compared with decrease in the naïve B cells. Furthermore, IL-1β and macrophage-colony stimulating factor (M-CSF) were predicted as novel candidate target genes for inflammatory storm whereas TNFSF13, IL-18, IL-2 and IL-4 seemed to be beneficial for the recovery of COVID-19 patients.

3.3 Transmission of SARS-CoV-2 by asymptomatic persons is implicated in crowd & family-clustered outbreaks

Multiple studies have found that there are asymptomatic SARS-CoV-2 infections in the process of crowds and family-clustered outbreaks. Among a family of six in Shenzhen who traveled to Wuhan from 29 December 2019 to 4 January 2020, five members were identified with COVID-19, including an asymptomatic 10-year-old boy [85]. A family members who traveled on 22 January 2020 from Wuhan to Guangzhou, China, through the high-speed rail tested positive for SARS-CoV-2, but only one developed clinical symptoms, and the other two members had no signs or clinical symptoms [86]. Asymptomatic COVID-19 patients can even become the source of infection in contagious outbreaks among families. SARS-CoV-2 transmission from an asymptomatic infected person returning home from Wuhan on 10 January 2020 was suspected as the cause of a family cluster epidemic of five members in Anyang, China [87].

3.4 Lung

ACE2 is shown to be localized to the lungs, as has one of the angiotensin receptors, AT1, but not AT2. There is a clear, the interaction of ACE2 and AT1 on lung protection in models of disease, including those caused by coronaviruses [88, 89, 90]. Genetic knock-out of AT1a receptor expression markedly improved lung function in mice with a genetic knockout of this receptor (Agtr1a-/- mice), confirming the function of Ang-II in lung health [91, 92].

ACE2 knockout mice developed more severe ALI in models that result in respiratory distress (Nagase et al., 2000). But injection of ACE2 show to protect mice with ALI [88].

Many researcher has demonstrated that the injection of SARS virus leads to an increase level of Ang-II in lung tissue and exacerbates ALI in mice. It is shown the viral spike from SARS inhibit ACE2 and may result in increases levels of Ang-II. The ACE gene that has been studied in details, the presence (insertion, I) or absence (deletion, D) of a 287 base pair sequence of alu within intron 16 of the gene that encodes ACE. The D genotype of ACE is associated with ARDS susceptibility and outcome, where DD genotype was associated with ARDS [93, 94], although this has not been demonstrated in all populations [95].

The same genotype of ACE it is shown too associated with higher ACE activity, which, result in lower Ang-II levels. More recent data on COVID-19 has demonstrated important differences in race on infection rates and severity [96, 97, 98].

3.5 Heart

The study in coronaviruses has demonstrated that a high percentage of patients have cardiac dysfunction, including cardiomyopathy and cardiac injury. In some publication it is shown a greater number of patients who are hospitalized with COVID-19 and demonstrating cardiac injury [99]. This cardiac dysfunction following the viral infection, is a temporary drop in ACE2 levels, due to ACE2 destruction as a result of the infection. Previously data indicates that the infection can result in ACE2 destruction, reduction in membrane-bound ACE2 and that ACE2 has a protective role in the heart [100, 101]. The disruption of ACE2 accelerates cardiac hypertrophy and shortens the transition period to heart failure in an Ang-II model of heart failure [102].

Patients who become infected with COVID-19 lose some of the pulmonary and cardiac protective mechanisms of ACE2 and Ang(1–7), due to viral binding and the resultant destruction of ACE2 following infection [101].

4. Discussion and conclusion

Here in this review we describe coronavirus disease 19 caused several acute respiratory syndrome. The SARS CoVID-19 infection emerged in December 2019. This virus belongs betacoronavirus genera and contain positive non-segmented RNA. The genome of CoVID-19 range between 27-32kDa; and have spherical and pleomorphic form. Replication cycle is divide into three phase: a) viral entry; b) RNA replication; c)exit from host cell.

Developing of new drug for patient treatment with CoVID-19 is impractical to face the pressing global challenge. Many clinical and research laboratory suggest to used drugs such as Favipiravir, Remedesivir, Lopinavir/ritonavir, Chloroquine, Hydroxychloroquine, Ribavirin, Tocilizumab, Ciclesonide, Niclosamide, High-dose intravenous immunoglobulin (IVIG) and Multidrug combinations.

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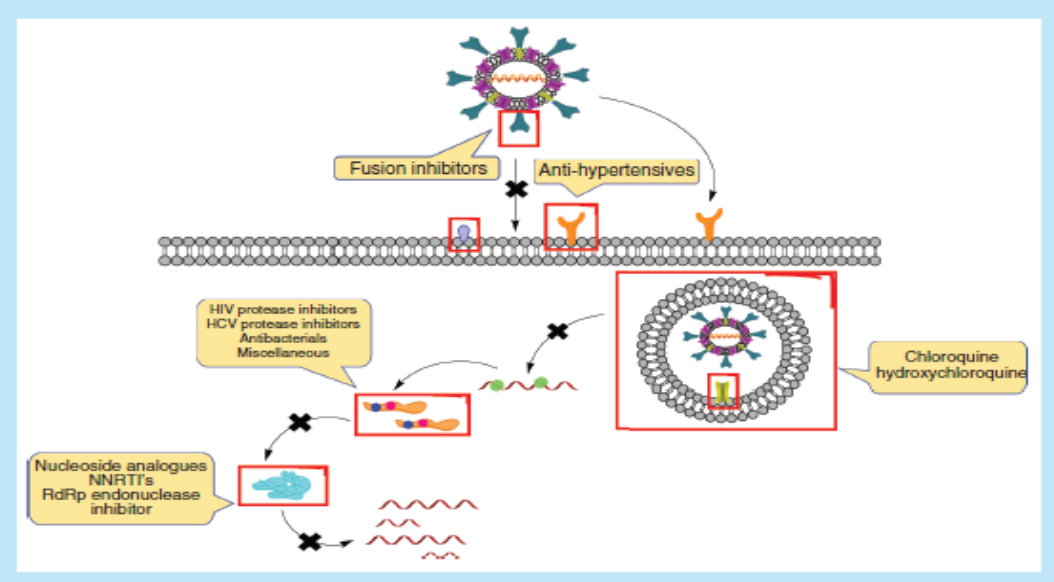
Graphical abstract:



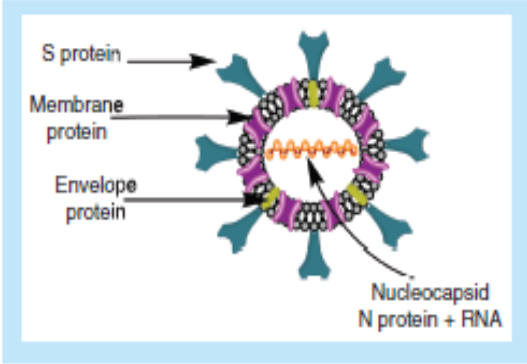


Fig 1. Various proteins associated with SARS-CoV-2

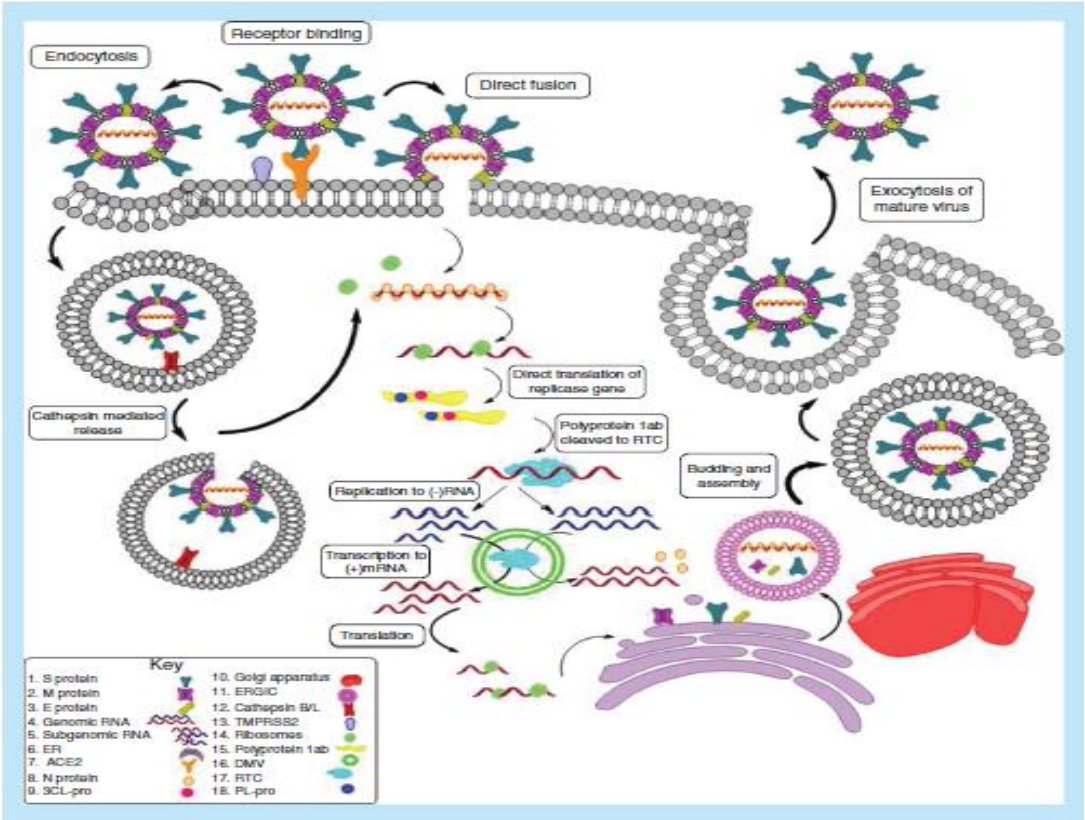


Fig 2. Replication cycle of SARS-CoV-2. DMV: Double membrane vesicle; ER: Endoplasmic reticulum; RTC: Replicase–transcriptase complex

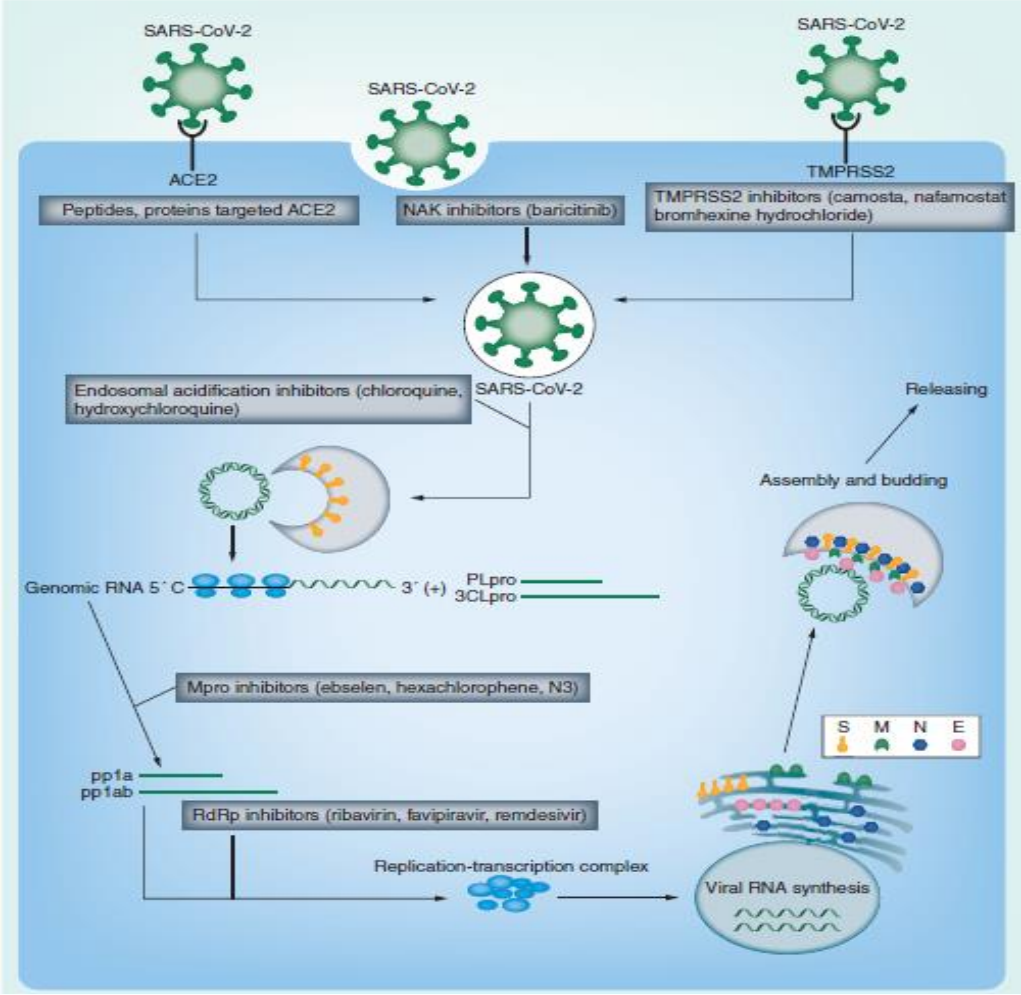


Fig 3. Potential drug targets and the corresponding inhibitors against SARS-CoV-2. E: Envelope; M: Membrane; N: Nucleocapsid; S: Spike.

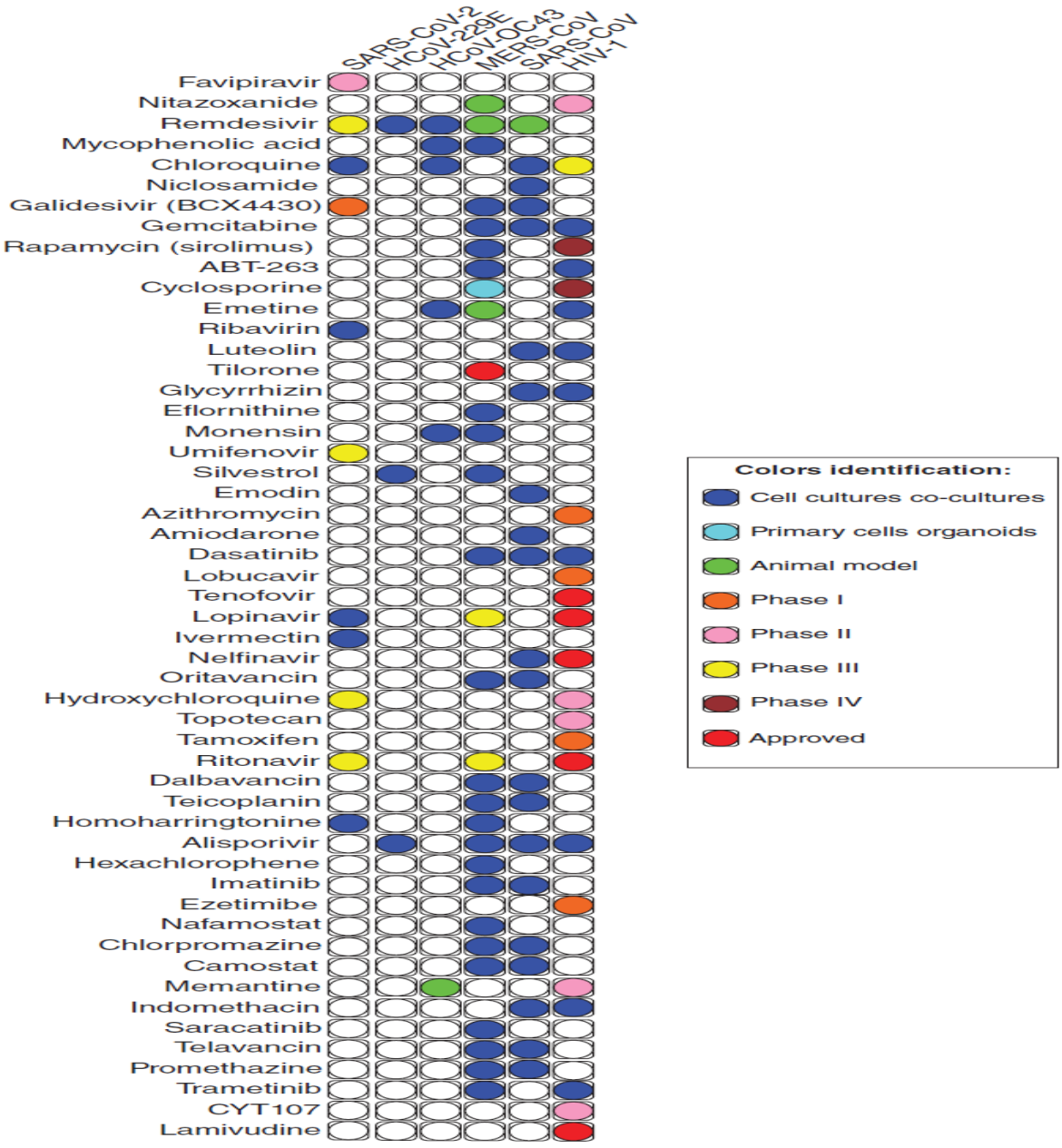


Fig 4. Advancement of research on selected drugs used against various types of viruses, and possibilities for their repurposing for SARS-CoV-2 therapy. The presented data are subject to current changes related to the introduction of individual drugs into experimental therapies (Pawełczyk and Zaprutko 2020).

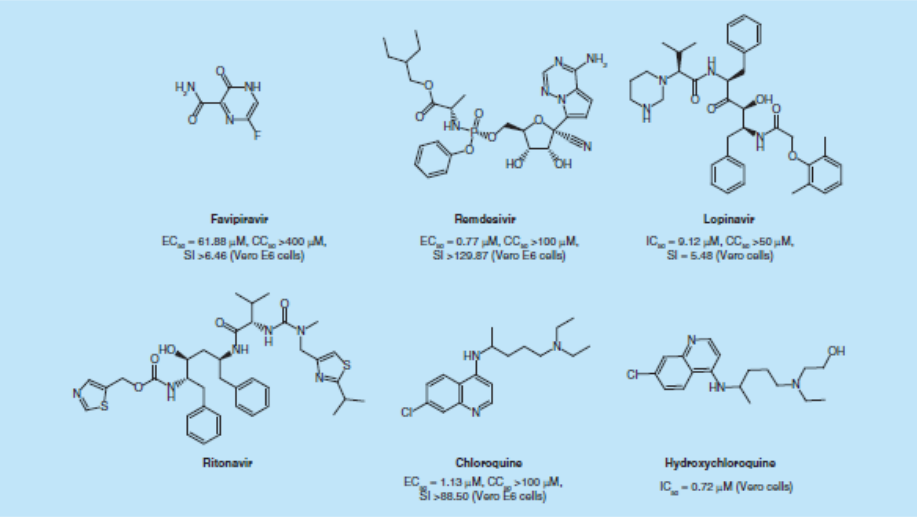


Fig 5. Structures and in vitro activities of repositioning antiviral drugs in clinic for SARS-CoV-2. CC50: 50% Cytotoxic concentration; EC50: Half maximal effective concentration; IC50: Half maximal inhibitory concentration; SI: Selectivity index

Table 1. Clinical trials of repositioning antiviral drugs for COVID-19.

Drug	Numbers of clinic trial	Status of clinic trial	Name of guideline
Favipiravir	14	Recruiting: 3 Not yet recruiting: 9 Active, not recruiting: 1 Enrolling by invitation: 1	Treatment of novel coronavirus disease in Japan (first edition)
Remdesivir	21	Recruiting: 10 Not yet recruiting: 5 Available: 2 Enrolling by invitation: 1 Suspended: 1 Terminated: 1 Completed: 1	Expert recommendations on treating patients during SARS-CoV-2 epidemic (France) Clinical management of COVID-19: medical treatment (Spain) Antiviral therapy for patients with novel SARS-CoV-2 coronavirus infection (Greece)
Lopinavir/ritonavir	53	Recruiting: 29 Not yet recruiting: 14 Active, not recruiting: 2 Enrolling by invitation: 3 Completed: 5	Diagnosis and treatment protocol for novel coronavirus pneumonia (trial version 7) Treatment of novel coronavirus disease in Japan (first edition) Expert recommendations for treating patients during the SARS-CoV-2 epidemic (France) Clinical management of COVID-19: medical treatment (Spain) Antiviral therapy for patients with novel SARS-CoV-2 coronavirus infection (Greece)
Chloroquine	57	Recruiting: 29 Not yet recruiting: 25 Enrolling by invitation: 3	Diagnosis and treatment protocol for novel coronavirus pneumonia (Trial Version 7) Expert recommendations on treating patients during SARS-CoV-2 epidemic (France) Drug treatment options for patients with COVID-19 (SARS-CoV-2 infection) (Netherlands) Antiviral therapy for patients with novel SARS-CoV-2 coronavirus infection (Greece)
Hydroxychloroq-uine	174	Recruiting: 80 Not yet recruiting: 72 Active, not recruiting: 4 Enrolling by invitation: 12 Completed: 3 Suspended: 3	Expert recommendations on treating patients during SARS- CoV-2 epidemic (France) Drug treatment options for patients with COVID-19 (SARS-CoV-2 infection) (The Netherlands) Antiviral therapy for patients with novel SARS-CoV-2 coronavirus infection (Greece)
Ribavirin	7	Recruiting: 3 Not yet recruiting: 2 Completed: 2	Diagnosis and treatment protocol for novel coronavirus pneumonia (trial version 7)
Darunavir	4	Recruiting: 2 Not yet recruiting: 1 Active, not recruiting: 1	Guidelines for the treatment and support management of patients with COVID-19 coronavirus infection (second edition; Italy)
Arb.i.d.ol	8	Recruiting: 3 Not yet recruiting: 3 Active, not recruiting: 1 Enrolling by invitation:1	Diagnosis and treatment protocol for novel coronavirus pneumonia (trial version 7) Expert recommendations on treating patients during SARS-CoV-2 epidemic (France)

Table 2. Multi-drug combinations for COVID-19 in clinical trials.

Combination drug	Mechanism of action	Registered trials
Ribavirin + lopinavir/ritonavir + INF-α	Nucleoside inhibitor + protease inhibitor + regulates the activity of the immune system	ChiCTR2000029387, ChiCTR2000029573
Ribavirin + lopinavir/ritonavir + IFN-α	Nucleoside inhibitor + protease inhibitor + regulates the activity of the immune system	NCT04276688
Ribavirin + interferon	Nucleoside inhibitor + Regulates the activity of the immune system	ChiCTR2000030922
Favipiravir + chloroquine	Pyrazinecarboxamide derivative viral RNA polymerase inhibitor + heme polymerase inhibitor	ChiCTR2000030987
Favipiravir + tocilizumab	Pyrazinecarboxamide derivative viral RNA polymerase inhibitor + anti-human IL-6 receptor	ChiCTR2000030894, NCT04310228
Lopinavir/ritonavir + arbidol	Protease inhibitor + hemagglutinin inhibitor	NCT04252885
Ganovo + ritonavir	Protease inhibitor	ChiCTR2000030472, ChiCTR2000030259, NCT04291729
Darunavir/cobicistat + thymosin α1; Lopinavir/ritonavir + thymosin α1	Protease inhibitor + stimulation of the development of precursor T cells	ChiCTR2000029541
Lopinavir/qitonavir + emtritabine/tenofovir alafenamide fumarate	Protease inhibitor + reverse transcriptase inhibitor	ChiCTR2000029468