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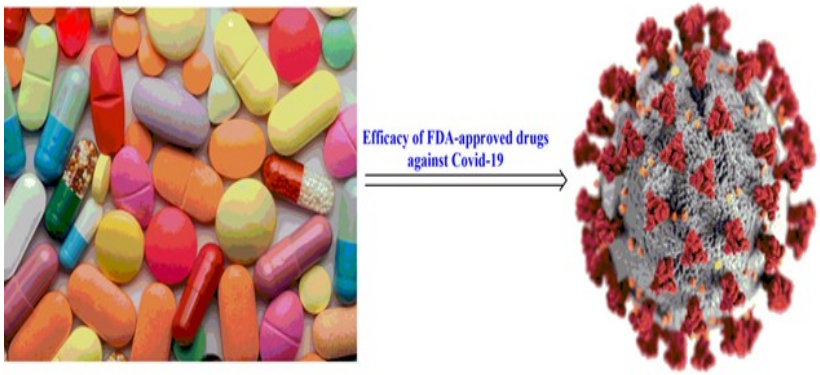
Potential Drug Candidates in Clinical Trials for the Treatment of Covid-19: An Updated Overview

Osmar Ignacio Ayala Cáceres [†], Fernanda Timóteo [†], Kristiane Fanti Del Pino Santos, Rafael Rodrigo Piva Vasconcelos, Marco Antonio Utrera Martines, Juliana Jorge*, and Haroon ur Rashid*

The coronavirus (SARS-CoV-2) emerged in December 2019 in Wuhan, China and by the end of April 2020, it spread to more than 200 countries worldwide. Particularly the USA, Brazil, Spain, Italy, France, Germany, UK, Turkey, Iran, and Russia were the most affected countries till December 2020. Currently, most of the researchers are in a continuous struggle to develop a vaccine or new drugs to combat Covid-19. There are more than 30 drug candidates including Western medicines, natural products, and traditional Chinese medicines, that have shown to exhibit some efficacy against this highly infectious virus. This review encompasses the potential efficacy of some key drugs recently tested against Covid-19. With the rapid spread of Covid-19 reaching a new level every day, there is an immediate need to find safe and effective measures to diagnose, treat, mitigate, and combat the disease. Looking at the alarming dimensions that the disease is acquiring, treatment strategies among the different drug systems are being investigated. Currently, clinical management includes infection prevention, control measures, and supportive care, including supplemental oxygen and mechanical ventilation when indicated. The pharmaceutical interventions evaluated for the treatment of Covid-19 include human immunoglobulin, interferons, chloroquine, hydroxychloroquine, arbidol, remdesivir, oseltamivir, favipiravir, carrimycin, methylprednisolone, bevacizumab, thalidomide, vitamin C, pyrodfenidone, darthviravir, bromexistone, ryrexavir, lopinavir, xiyanping, and traditional Chinese medicine. But still, the researchers are struggling to discover the most effective drug for the treatment of the current pandemic of Covid-19.

Graphical abstract



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Institute of Chemistry, Federal University of Mato Grosso do Sul, Campo Grande, MS, Brazil. [†] These authors have contributed equally. Corresponding author. E-mail: **ju.jorge@yahoo.com.br** (J. Jorge); **haroongold@gmail.com** (H. ur Rashid).

1. Introduction

Coronavirus disease (Covid-19), a virus-related contagious respiratory illness is triggered by Severe Acute Respiratory Coronavirus Syndrome 2 (SARS-CoV-2) which caused a global pneumonia pandemic in 2020. It originated in December 2019 in Wuhan, Hubei, China, and was reported to the World Health Organization (WHO) on December 31 [1–3]. The disease spread very quickly outside the Chinese borders, affecting most of the world, becoming no longer an outbreak, but an epidemic and, in March 2020 with 125,048 cases and 4,614 deaths, WHO declared it as a pandemic. Covid-19 had spread to about 220 countries worldwide, causing more than 170 million confirmed cases and 3.7 million deaths till June 2, 202 [1–4].

All populations were vulnerable to this extremely infectious virus, regardless of sex, age, or race. Therefore, the number of infected people continues to increase over time. The proportion of severe cases remains high, and now many countries are entering the second wave of infection, demanding effective regimes for this highly contagious disease. This scenario requires a rapid discovery of efficient drugs or vaccines to combat Covid-19 and has emerged as one of the most challenging tasks for scientists all over the world [1,5].

1.1 Sars-CoV-2 and its infectious mechanism

To obtain a probable genomic structure for SARS-CoV-2, previously known information about the sequences of the coronavirus's genome similar to SARS-CoV-2 were utilized. Moreover, the structure and function of proteins were used to determine the trajectories and identify interactions with host proteins. In addition, this information was used to support the search for efficient drugs and vaccines for combating and avoidance of Covid-19 [6]. For instance, it is possible to elucidate the replication of SARS-CoV-2 based on the SARS-CoV and Middle East Respiratory Syndrome-related coronavirus (MERS-CoV) mechanism since structural and non-structural proteins in SARS-CoV-2 are analogous to those found in the two viruses [7,8].

The structures of protein found in several SARS, MERS, and other associated coronaviruses, along with their biological connections, have been exploited to deliver broad structural genomics and interatomic route for Sars-CoV-2 and imply probable differences and similarities with the correlated SARS coronaviruses. The Sars-CoV-2 virion consists of 16 non-structural proteins which make up a polyprotein, along with 13 open reading frames (ORFs): Surface, ORF3a, ORF3b, Envelope, Membrane, ORF6, ORF7a, ORF7b, ORF8, Nucleocapsid, ORF9a, ORF9b, and ORF10. The three pathological species whose proteins share a high similarity are steadily the same: human SARS (SARS-CoV), bat coronavirus (BtCoV), and a bat beta-coronavirus (BtRf-BetaCoV) [6,8,9].

Coronavirus class is named after their look under the electron microscopy technique. They appear to be covered by spike structures surrounded by a crown-like assembly owing to the existence of peak glycoproteins in their envelope (Fig. 1) [10]. The SARS-CoV-2 is a beta-coronavirus that contains a single-stranded RNA genome like MERS-CoV and SARS-CoV. The ORF1a/b region covers two-third of the viral RNA genome, and this region translates two polyproteins (pp1a and pp1ab) in addition to encoding many non-structural proteins (nsp). This region of the virus genome also encodes accessory proteins and vital structural proteins together with spike glycoprotein (S), small-envelope protein (E), matrix protein (M), and nucleocapsid protein (N). The spikes consist of a single-pass transmembrane anchor, a large ectodomain, and a short intracellular tail. The ectodomain consists of two subunits S1 and S2. Homotrimers of protein S support the construction of the spikes which have a fundamental part in their connection with host receptors. The glycoprotein M performs three main functions, (a) provides a form to virions, (b) helps in promoting membrane curvature, and (c) supports the attachment to the nucleocapsid. Glycoprotein E plays a crucial role in virus construction and pathogenesis. Glycoprotein N contains two domains of connection with the virion RNA genome, and it appears that this protein can bind to non-structural protein 3 (nsp-3), aiding to bind the genome to Replication-Transcription Complexes (RTCs) and the packing of the genome involved in virions [6,11].

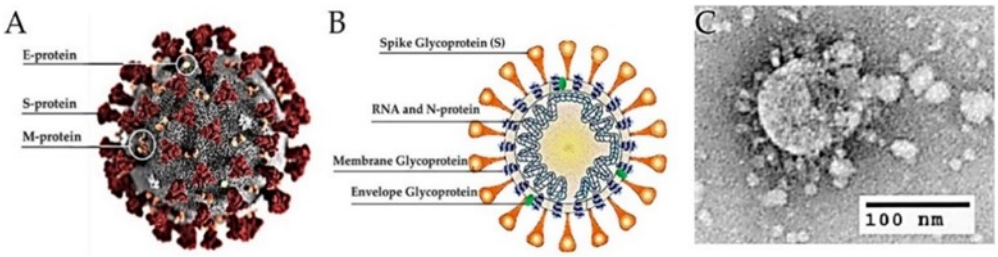


Fig. 1. The SARS-CoV-2 structure showed in a design created by the Centers for Disease Control and Prevention (CDC) (A), in a schematic representation (B), and an image of the virion seen under electron microscopy technique (C). (Reproduced with permission from T. M. Abd El-Aziz et al. Infect. Genet. Evol. 2020, 83, 104327, © 2020 Elsevier) [10].

Existing antiviral drugs against coronavirus (CoV) diseases were designed to target protein S, 3C-like (3CL), and papain-like (PLP) proteases. Viruses with protein S mutations are susceptible to evade targeted therapy using diverse host cell receptor binding patterns, on top of that MERS coronavirus displays antibody-dependent enhancement (ADE) effects of protein S antibodies, which remains a severe restriction for antiviral techniques. Antiviral protease inhibitors might act nonspecifically on the homologous cell protease, leading to host cell toxicity and serious side effects. Consequently, new antiviral approaches are required to fight acute respiratory infections triggered by the new SARS-CoV-2 coronavirus [6,8,12].

The N protein is a multifunctional RNA-binding protein needed in the course of transcription and replication of viral RNA and plays several essential roles in the formation of spiral ribonucleoproteins in the course of packing the RNA genome, controlling the synthesis of viral RNA during replication,

transcription, and regulating the metabolism of host cells. Results of *in vitro* and *in vivo* assays showed that N protein is attached to the leading RNA and is crucial to sustaining the highly ordered RNA conformation apt for viral genome replication as well as transcription. Further studies have shown that N protein regulates host-pathogen relations, for instance, actin reorganization, host cell cycle evolution, besides apoptosis. Additionally, N protein has an elevated immunogenicity rate and is widely expressed through an infectious process, which may induce protective immune reactions versus SARS-CoV and SARS-CoV-2. Coronavirus N protein consists of three extremely well-maintained domains: (a) N-terminal RNA binding domain (NTD), (b) C-terminal dimerization domain (CTD), and (c) a central domain with Ser/Arg-rich linker (SR), which is naturally disarranged. Earlier reports showed that NTD controls the binding to RNA, CTD allows oligomerization, and the SR-rich linker leads to elementary phosphorylation. N-NTD CoV proteins were associated with the final portion of the viral RNA genome by electrostatic interactions [6,8].

An understanding of the characteristics of the virus genome is extremely important for the exploration of specific agents to obstruct the replication, transcription, and viral assembly. For instance, it has been reported that a model for better understanding of the molecular exchanges and regulating the binding to SARS-ribonucleotides should be the crystalline structure of the N-terminal domain of the SARS-CoV-2 nucleocapsid. This discovery will assist in the discovery of novel specific drugs for viral N protein, SARS-CoV-2 viral replication, in addition to the highly related SARS-CoV virus [6,8].

The infectious mechanism of SARS-Cov-2 (Fig. 2) initiates when the virus reaches the host and binds to the cells through interactions between glycoprotein S and angiotensin-2, converting enzyme (ACE-2) receptors, which determines the virion tropism. Aided by cathepsins and serine transmembrane protease 2 (TMPRSS2), the virion enters the cytosol, causing the division of protein S at two spots. The first one results in the separation of the receptor-binding domains (RBD) and the fusion domain of protein S, whereas the second division displays the fusion peptides to endosomes. Then, six spiral packs are shaped, causing the discharge of the virions along with the cytoplasm. Subsequently, the virus gets attached to the host, and the replication cycle begins. During replication, the replication gene is translated into the virus genomic RNA, which is encoded by ORF1a and ORF1b. It then expands to polyprotein 1a and 1b (pp1a and pp1b) and is expressed by the unstable '5UUU AAC-3' sequence and RNA pseudo-node, which causes the ribosomal displacement, interrupting ribosomal stretching. This RNA sequence also acts as mRNA, expressing structural and accessory proteins. In the end, the virus disperses through the body whereas, proteins S1, M, and E are translated, helping the virion to go into the endoplasmic reticulum and transitional compartments of the endoplasmic-Golgi reticulum (ERGIC). Protein M commands protein-protein interaction activates virus-like particles (VLPs) with the help of protein E and promotes the corona envelope construction. Whereas the N protein endorses the development of VLPs and their fusion to the ERGIC, resulting in the assembly of the SARS-CoV-2. Viral exocytosis occurs as a result of the exchanges between healthy and infected cells through the Golgi apparatus and vesicles. Ultimately, oversize cells are produced, and the new virions are released from these cells to infect other cells [7,8,11–13].

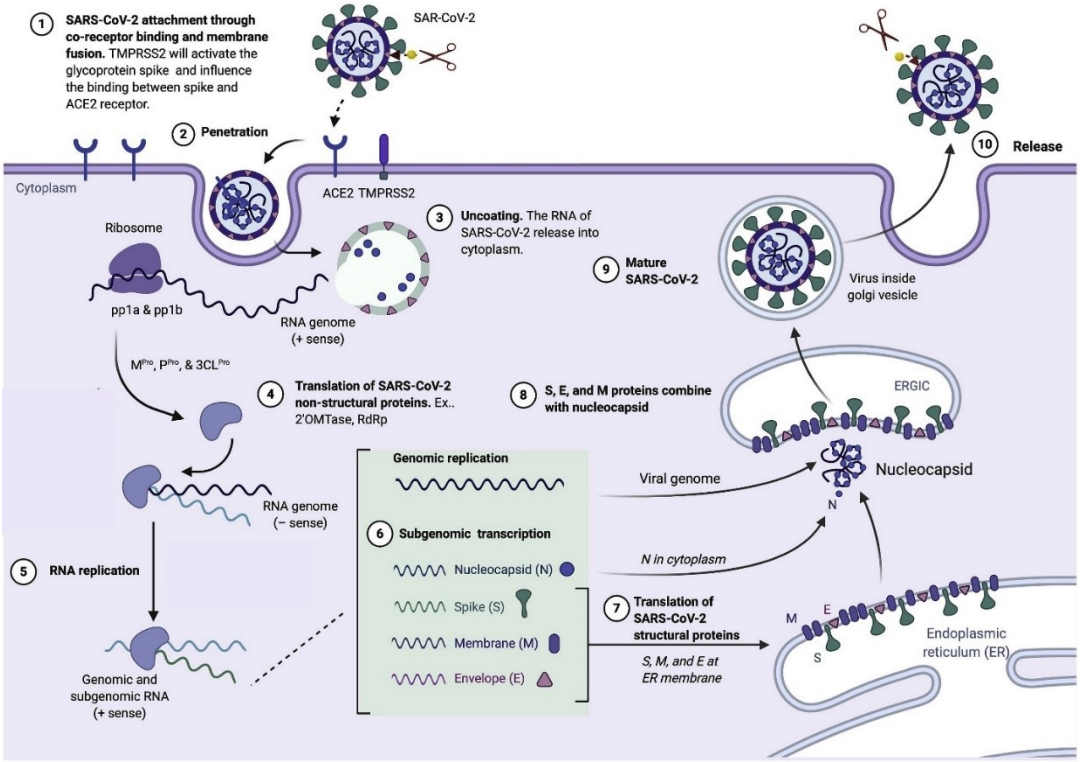


Fig. 2. The infectious mechanism of SARS-CoV-2. (Reproduced with permission from A. Frediansyah et al. *Clin Epidemiol Glob Health*. 2020, 9, 90-98, © 2020 Elsevier) [7].

1.2 Epidemiology

Currently, it is known that the incubation phase of the SARS-CoV-2 virus varies between 1 to 14 days, with an average period of 6 days. Some studies have shown that the incubation phase can last up to 24 days [13–15]. A higher time

of incubation has significant consequences regarding isolation and spread prevention policies. The virus is transmitted mainly by massive droplets spread in the air through the sneezing and coughing of the infected person, and also can be located in feces and blood that has raised questions about other means of transmission [13].

Data from the initial outbreak demonstrated exponential growth showing that the pandemic duplicate in size every 7.4 days, and the basic reproduction number (R0) projected by most studies ranges from 2.2 to 3.6, an average higher than that of SARS [14,16,17]. However, for similar geographic regions, it is possible to estimate different R0 values by several methods and assumptions. This knowledge leads to the conclusion that more data is needed to determine a more accurate R0 value [17].

At the time of writing this review article, according to the WHO panel, there are already over 93 million confirmed cases in the world, and more than 2 million deaths at a 2.16% fatality rate. USA is the country with the largest number of confirmed cases (23,344,423 cases, with 389,084 deaths, with a fatality rate: 1.67%). Other countries with more cases are India (10,557,985 cases, 152,274 deaths, fatality rate: 1.44%), Brazil (8,393,492 cases, 208,246 deaths, fatality rate: 2.48%), Russia (3,568,209 cases, 65,566 deaths, fatality rate: 1.84%), United Kingdom (3,357,365 cases, 88,590 deaths, fatality rate: 2.64%), France (2,846,971 cases, 69,753 deaths, fatality rate: 2.45%), Italy (2,368,733 cases, 81,800 deaths, fatality rate: 3.45%), Spain (2,211,967 cases, 53,079 deaths, fatality rate: 2.40%), Germany (2,033,518 cases, 46,419 deaths, fatality rate: 2.28%), Colombia (1,870,179 cases, 47,868 deaths, fatality rate: 2.56%), Argentina (1,783,047 cases, 45,227 deaths, fatality rate: 2.53%), Mexico (1,609,735 cases, 139,022 deaths, fatality rate: 8.63%), Turkey (1,566,327 cases, 23,832 deaths, fatality rate: 1.52%), Poland (1,435,582 cases, 33,355 deaths, fatality rate: 2.32%), South Africa (1,325,659 cases, 36,851 deaths, fatality rate: 2.78%). The country with the highest fatality rate is Mexico (8.63 %) followed by Iran (1,324,395 cases, 56,717 deaths, fatality rate: 4.28%) [18].

Like any other emerging infectious disease, all races and ages become vulnerable, meaning SARS-CoV-2 can infect people of any age, but middle-aged and older people are generally at higher risk [10,15,17]. In April, most data reports of hospitalized patients with the clinical diagnosis of Covid-19 showed that the mean age was between 48 and 58 years [10].

Although Covid-19 has been reported in elderly patients, older elderly patients appear to be more susceptible to infection. Infection rates are lower among younger people (children and adolescents) and may deviate between 0.8% and 4.0% besides the high rate of asymptomatic infection at this age [17].

In continental China, 30-65 years old account for 71.45% of the infected people, whereas children under ten years represent 0.35%. Senior citizens and people with previous disorders like diabetes, asthma, cardiovascular disease, and cancer, may well be more susceptible to SARS-CoV-2. Besides, smoking and obesity also represent susceptibility factors. People in close contact with infected patients or symptomatic subclinically infected people are part of the population at higher risk of infection, which is also considered by health professionals and family members of patients [15].

The high death rate in older patients is already a recognized fact. Advanced age has likewise been related to increased death from primary diseases, with fatality rates between 8-15% among those aged 70 to 80 years or older, a similar pattern was found in Italy, with a fatality rate of 12-20% among the patients of the same age [10,17].

The accomplishment in preventing Covid-19 among older and people with previous disorders regulates the fatality rate in different nations. The first Chinese reports, for example, exhibited a death rate three times higher in aged patients, particularly for those over 80 years old. An Italian study demonstrated that death rates of patients older than 65 in Intensive Care Units (ICU) were 26% and 36%. The average number of days between symptoms onset and death was reported to be shorter too in older patients [17].

In Italy, another report showed that several primary conditions could have increased the mortality risk among patients with an average age of 79.5 years. Among those who died, 25.4% had ischemic heart disease, 27.4% had diabetes, 15.7% had cancer, 18.9% had atrial fibrillation, 5.2% had dementia, and 7.4% had a cerebral vascular accident [10,17]. In the USA, 67% of the patients diagnosed with Covid-19 were nearly 65 years old, similar to China, where 80% of deaths occurred in patients 65 years old and over [10].

The most predominant comorbidities are hypertension, diabetes mellitus, cardiovascular and respiratory diseases. These comorbidities have been detected in critically ill patients, and also appear to be the underlying diseases most frequently identified among hospitalized patients. Reports indicate that a previous comorbid illness increases the mortality rate by 10.5% for cardiovascular diseases, 7.3% for diabetes, 6.3% for chronic respiratory diseases, 6.0% for hypertension, and 5.6% for cancer [17].

It seems that SARS-CoV-2 can also discriminate gender, men are more susceptible to test positive as well as to expire from Covid-19. This tendency was first detected in China, where an investigation found a fatality rate of 2.8% in men versus 1.7% in women. This trend has also been observed in France, Germany, Iran, Italy, South Korea, and Spain [10,13,19,20]. It is still unclear why the virus can strike men more than women. In several countries, especially China, men smoke more than women, increasing their susceptibility for the development of more severe forms of Covid-19. Also, women usually have better and stronger immune responses than men [10,13,19].

A hypothesis came up with a study of blood mononuclear cells, suggesting that the decreased T-cell epigenomic signature and the increased function of monocytes and cytotoxic cells are higher in elderly males than in elderly women. Age-linked immunological variations and sex differences occur in the first moment around the late 30s, whereas a second variation occurs after age 65. Therefore, older men would be more vulnerable to infectious illnesses of high pro-inflammatory and low adaptive immune responses than older women [20].

The current fatality rate of SARS-CoV-2 (2.55%) is lower than those reported for SARS-CoV (10%) and MERS-CoV (37.1%), although the number of confirmed cases is several times higher since SARS-CoV-2 is transmitted by asymptomatic or mild infected people, which explains the high spread rate of the viral pandemic [21].

1.3 Clinical characteristics

In general, the initial symptoms of SARS-CoV-2 infection include ageusia and anosmia. Other common symptoms are fever, dyspnea, cough, myalgia, and tiredness. SARS-CoV-2 infection symptoms might also include ataxia, dizziness, headache, loss of consciousness, diarrhea, subacute thyroiditis, nausea, and vomiting. In critical cases, acute respiratory distress syndrome, or multiple organ failure, skin

disorders such as rashes and urticaria can occur as well [10,12,13,19].

Serological test findings showed 70% lymphopenia, 58% prolonged prothrombin time, and 40% elevated lactate dehydrogenase. Chest radiographs and computerized tomography (CT) scans are characterized by irregular bilateral infiltrates showing infiltrations in ground glass [13,19].

There are pieces of evidence of the presence of hyaline membrane formation, interstitial mononuclear inflammatory infiltrates, and multinucleated oversize cells, similar to the findings of SARS or MERS infections [10,13]. Most patients have a minor infection, but it is vital to explain the spectrum of the disease, understanding asymptomatic and severe cases, associated risk factors for the illness progression, and mortality rate [13].

Kim et al. (2020) reported that patients with moderate to severe symptoms of SARS-CoV-2 infection were admitted to a community health service designed for quarantine in South Korea. The most common symptoms noted in the patients were cough with or without hyposmia and sputum. Whereas one-fifth of the patients with mild infection were asymptomatic. Additional research on the contribution of asymptomatic or mildly symptomatic people is vital for the effective management of the spread of this pandemic [22].

1.4 Management and prevention

In a pandemic context, prevention and management of the outbreak are crucial issues. It needs collective efforts by the population and the government. In this case, simple measures become very assertive and effective as to recognize the source of spread and control the infection through diagnosis, reports, isolation, quarantine suspected of being exposed to the virus or disease and start treating patients early [12,23].

Moreover, it becomes imperative to break the transmission cycle by following hygienic practices, such as washing hands, disposing of nasal secretions, using disinfectants for hands, wearing face masks, and avoiding physical contact as much as possible [12,20,23,24]. Social isolation prevents contact with infected or asymptomatic people, and the facial coverage protects from aerosol droplets, although improper use and disposal of masks can increase the risk of infection [20].

Protection of the more vulnerable population might be a suitable way of management and prevention. In other words, protect older people, pregnant women, emergency patients, and those who are on hemodialysis and cancer treatment, and diabetics [12].

Among supplements, those with therapeutic potential are the nicotinamide riboside (NR), which increases the precursors of nicotinamide adenine dinucleotide phosphate (NADP), a coenzyme needed for a variety of metabolic pathways. Dietary supplements such as vitamin A, vitamin C, Omega-3 fatty acids, polyphenols, and carotenoids have anti-inflammatory and antioxidant features. Supplements such as vitamin D may reduce exposure to SARS-CoV-2 by impeding ACE-2 expression. Additionally, Zinc as a supplement increases innate and adaptive immunity and, therefore, impedes the replication of the virus. Again, all these supplements have their benefits, but more studies are needed to confirm whether they can act as antiviral drugs [12,20].

1.5 Treatment: Up to this date

After almost a year of the prevalence of the Covid-19 outbreak, there is still an urgent demand to discover safe and effective actions to cure and fight the disease. Therefore, treatment strategies among the different drug mechanisms are being investigated [11]. Currently, clinical management is based on preventive measures and supportive care, with supplemental oxygen and mechanical ventilation when necessary [10].

The pharmaceutical interventions for treatment include drugs and methods like human immunoglobulin, traditional Chinese medicine, herb medicine, interferons, chloroquine, hydroxychloroquine, arbidol, remdesivir, oseltamivir, favipiravir, carrimycin, methylprednisolone, bevacizumab, thalidomide, vitamin C, pyrodfenidone, darthviravir, bromexistone, ryrexavir, lopinavir, and xiyanping [3].

The effects of synthetic RNA-dependent RNA polymerase inhibitors, protease inhibitors (antivirals, antibiotics, anti-inflammatories, antimalarial drugs, antiparasitic drugs, corticosteroids, etc.), teicoplanin, and other glycopeptides are in trials. Herb medicines like extracts have also been studied (*Lindera aggregata*, *Lycoris radiata*, *Artemisia annua, Pyrrosia lingua*, and *Isatis tinctoria*). Also, vaccines are under development (such as attenuated DNA-based, protein-based, virus-like particles, mRNA-based). Besides, nutraceuticals in RNA virus infection, convalescent plasma therapy, therapies using monoclonal and polyclonal antibodies, multiple treatment strategies (using different antibodies and RNA-based therapies) are under investigation [3,10,31,11,14,25–30].

Probably the best plan to fight against SARS-CoV-2 might be an efficient vaccine, which stimulates the immune system to deliver antibodies against viral proteins or T cells that can destroy infected cells [28]. Although numerous research groups are working to synthesize a vaccine, it is practically unquestionable that there will be no vaccine available in the next few months. Therefore, there is more pressure to find an effective drug against the virus, whether a new one or among the already existing drugs [10,28]. Although numerous clinical trials have been carried out, none of the tested drugs is still totally effective for Covid-19. Alternatively, new drugs such as small inhibitors, and ACE2 peptide inhibitors are expected to treat SARS-Cov-2 infection [30].

Therefore, the main objective of this review is to shed light on research about the drugs currently in clinical trials and deliberate about their potential effects against SARS-Cov-2 infection to achieve a critical discussion in treatment and therapy efficacy.

2. Covid-19 Treatment: Drugs under Evaluation

2.1 Atazanavir

Originally used for HIV treatment [32] atazanavir (Fig. 3) had its use authorized in the United States and Europe in 2003 [33], acts as the Main protease (M^{PRO}) inhibitor [34] and its effect is enhanced when used in combination with ritonavir to treat HIV [35].

Coronaviruses have two enzymes involved in the replication process; they are papain-like protease (PL^{PRO}) and chymotrypsin-like protease ($3CL^{PRO}$). The second enzyme can also be called the Main Protease (M^{PRO}) [36] which is directly involved in the viral reproduction mechanism; therefore, it becomes an important target in the development of antiviral drugs [37]. The length of coronaviruses genomic RNA is

approximately 30,000 nucleotides and comprises about six open reading frames (ORFs). Two important polyproteins (PP), pp1a and pp1ab are traduced directly by the first ORF, and these PPs and polyproteins go through the proteolytic process by the M^{PRO}, giving rise to 16 nonstructural proteins (NSPs) [36]. These NSPs are part of the production process of subgenomic RNAs that codify four leading structural proteins namely, membrane (M), envelope (E), spike (s), and nucleocapsid (N) proteins. This context enables M^{PRO} to play a fundamental role in the coronavirus cell cycle [38].

The SARS-Cov-2 M^{PRO} was mapped, its crystal structure and active sites were determinated [39] and a screening of the compounds was carried out using molecular docking, this technique is a computer simulation used to predict the conformation of a complex formed between a ligand and the binding site of the target (M^{PRO}), and the conformational energy of the resulting complex is evaluated [40]. Several studies were performed to identify the substances that bind to M^{PRO} active site more efficiently, and thus be able to inhibit its action [41].

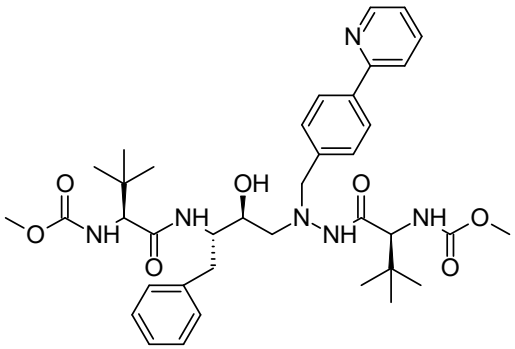


Fig. 3. Chemical Structure of atazanavir.

Table 1 shows the results obtained through molecular docking. Data analysis indicates that when more negative is the value, the more efficient is the M^{PRO} inhibition. These results confirm that atazanavir has the potential to act as an efficient SARS-CoV-2 M^{PRO} inhibitor as compared to other different drugs tested.

Table 1. Results were obtained via computer simulation performed for atazanavir using different types of software and methods. (A) Studies with the reference value, and (B) Studies tested.

Molecular Docking results were obtained for Atazanavir using different methods						
	Calculation method of electrostatic interactions	**Software**	**Reference value**	**Atazanavir**	**Ref.**	
A)	Particle Mesh Ewald	DOCK 6.9	Lopinavir (-59.87 kcal/mol)	- 65.49 Kcal/mol	[34]	
	GMX Energy (tool from Gromacs software)	GROMACS	-7.21 kcal/mol (UAW 247 inhibitor of M^{PRO})	-6.0 kcal/mol	[40]	
	CHEMPLP Algorithm	PLANTS	<-91.00	-105.72	[42]	
	Calculation method of electrostatic interactions	**Software**	**Reference value**	**Atazanavir**	**N.º drugs tested**	**Ref.**
B)	LIBDOCK	Discovery studio 2020	196.615 (1st)	182.122(3rd)	16	[43]
	Desmond package	AutoDock 4.2.6	-13.24 kcal/mol (1st) - Atazanavir	-13.24 kcal/mol (1st) - Atazanavir	10	[44]
	Molecule transformer-drug target interaction (MT-DTI)	-	94.94 nM (1st) - Atazanavir	94.94 nM (1st) - Atazanavir	7	[45]
	Particle mesh Ewald/ LINCS algorithm/ CHARMM-GUI	GROMACS	-7.9 kcal/mol (1st) – Dasabuvir	-7.3 kcal/mol (3rd) - Atazanavir	43	[46]
	CHARMM36m	AutoDock Vina	-8.8 kcal/mol (1st) - Atazanavir	-8.8 kcal/mol (1st) - Atazanavir	10	[47]

* In this case, the higher the value the better.
** Out of the 43 drugs, only 7 were linked to M^{PRO}, among which Atazanavir had the third-best result.

Reports using experimental assays to evaluate the action of atazanavir against SARS-Cov-2 were considered and the results showed half-maximal effective concentration (EC_{50} values) of 9.36 μM [48], and 2.0 ± 0.12 μM [49] whereas another study didn't show any activity of atazanavir [50]. In consultation with the clinicaltrials.gov database, three records of clinical studies using this drug were found under registration numbers NCT04459286, NCT04452565, and NCT04468087.

2.2 Daclatasvir

Developed for use in the treatment of hepatitis C virus (HCV) [51], daclatasvir (Fig. 4) acts as an inhibitor of a phosphoprotein, namely NS5A against HCV of genotypes 1-6, preventing its replication [52].

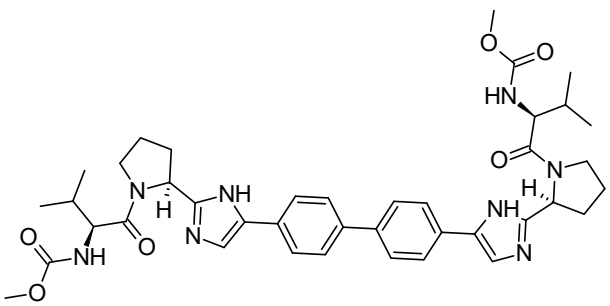


Fig. 4. Chemical Structure of daclatasvir.

Since daclatasvir is approved for commercial use, virtual screening studies were performed to predict the possible action of daclatasvir against SARS-Cov-2 via molecular docking. The replication and gene transcription process of coronavirus involves an enzyme i.e. RNA-dependent-RNA-polymerase (RdRp) [53], so the analyses by molecular docking were carried out to evaluate the binding affinity of daclatasvir and RdRp, some of the key findings are summarized in Table 2.

Table 2. Data were obtained from the computer simulation performed for daclatasvir using different types of software and methods to evaluate its binding affinity with RdRp protein.

Calculation methodz of electrostatic interactions	Software	Reference value	Daclatasvir	N. º drugs tested	Ref.
Consensus scoring (viz. DSX + X-Score + NNScore and RF-Score-VS)	AutoDock Vina	Asunaprevir (1st)	Daclatasvir (4th)	91	[54]
PyMOL and Chimera	AutoDock Vina	-9.9 (1st) - Beclabuvir	-8.4 (3rd) - Daclatasvir	70	[55]
MM/GBSA	Amber	15.89 (1st) – Decitabine	45.46 (12th) - Daclatasvir	50	[56]
-	Drug Discovery Studio	-8.2 (1st) – Ergotamine	-7.7 (7th) - Daclatasvir	26	[57]

Furthermore, *in vitro* tests were performed to evaluate daclatasvir activity versus SARS-Cov-2. In a study, Vero E6 cell line was used, and the results showed that daclatasvir had activity only at a concentration higher than 100 µM, whereas better results were exhibited by remdesivir (EC_{50} = 4.082 µM) and simeprevir (EC_{50} = 4.269 µM) [58]. Daclatasvir also suppressed the generation of infectious SARS-CoV-2 virus in Vero cells, hepatoma, and type II pneumocytes, with its EC_{50} of 0.8, 0.6, and 1.1 µM, respectively [59].

A randomized clinical trial was conducted in an Iranian hospital to evaluate the effects of sofosbuvir and daclatasvir on 66 Covid-19 patients with medium and severe symptoms. The preliminary results of the trial showed a decrease in the hospitalization time of the patients. The control group had 8 days of hospitalization, whereas the tested group had 6 days [60]. Another encouraging work compared clinical treatments of sofosbuvir/daclatasvir and ribavirin. In this study, 67 Covid-19 patients were divided into two groups, and the first group of patients (treated with sofosbuvir/daclatasvir) presented a hospitalization median of 5 days, and mortality rate of 9% versus the hospitalization median of 9 days, and mortality rate of 33 % for the second group of patients (treated with ribavirin) [61].

2.3 Favipiravir

Discovered by Toyama Chemical Co., Ltd., favipiravir (**Fig. 5**) acts against the influenza virus through inhibition of RdRp, which plays a key role in the replication of genetic material of the influenza virus and many other RNA viruses. The drug undergoes a Phosphoribosylation process to form favipiravir ribofuranosyl-5B-triphosphate, whose active form is recognized to inhibit the action of RdRp. The inhibitory action of favipiravir against several types of influenza and other RNA viruses is attributed to the RdRp domain that is maintained in several RNA viruses [62,63]. SARS-CoV-2 is also a single-strand positive RNA virus [64]. For this reason, the researchers are interested to investigate this drug in the treatment of Covid-19.

Table 3 summarizes the *in vitro* tests of favipiravir versus SARS-Cov-2 with its EC_{50} values ranging from 61.88 µM to 207.1 µM in Vero 6 cell line**.** The second and third columns represent the half-cytotoxic concentration (CC_{50} values), and the selectivity index, respectively. Selectivity index is the ratio between the CC_{50} values and EC_{50} values. Favipiravir showed weaker *in vitro* antiviral activity as compared to other compounds such as lopinavir (EC_{50} = 27 uM; SI = 1.9) and remdesivir (EC_{50} = 23 uM; SI >4.3) [65]. Moreover, a report was found in the literature confirming that *in vitro* studies did not identify the antiviral activity of favipiravir [32].

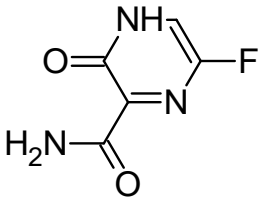


Fig. 4. Chemical structure of favipiravir.

Table 3. *In vitro* antiviral studies of favipiravir against SARS-CoV-2, using Vero 6 cell line.

EC_{50}	CC50	SI	Ref.
>100µM	631µM	<6.31	[66]
> 100 µM	> 100 µM	-	[65]
32 µg/mL	>78.5µg/mL	-	[67]
> 64 µM	> 64 µM	-	[68]
207.1 µM	-	-	[69]
61.88 µM	> 400 µM	<6.46	[70]

In vivo studies carried out in a hamster model indicated that high doses of favipiravir would be necessary to cure Covid-19, however, its use as prophylaxis has shown promising results [67].

A clinic open-label comparative controlled study was conducted to compare two therapies consisting of favipiravir (FPV) and lopinavir/ritonavir (LPV/RTV) against coronavirus. The study was conducted with 80 patients, 45 of whom received LPV/RTV treatment, and the other 35 received FPV. The FVP group presents a median time of viral clearance of 4 days versus 11 days of LPV/RTV group [71].

A comparative study between the action of FVP and arbidol was carried out on 240 patients. The data showed no significant difference in the recovery rate on day 7 of treatment, although FVP significantly improved the symptoms of fever and cough [72].

A recently published research was carried out to optimize the dose of FPV to treat Covid-19. The data showed that the FPV-tested group presented two-fold negative PCR tests for Covid-19 in comparison to the control group. Based on the results of clinical trials in phases II and III, FPV use has been authorized by the Russian Ministry of Health to treat Covid-19 to date [73].

Further randomized studies of FPV in combination with other compounds to cure Covid-19 are in progress (favipiravir + interferon-α, ChiCTR2000029600, favipiravir + baloxavir, ChiCTR2000029544), and are registered with the Chinese Clinical Trial Registry [74]. Additionally, 38 more studies are registered on the clinictrials.gov platform and are summarized in Table 4.

2.4 Clofazimine

First described in 1957 [75], clofazimine (Fig. 6) has an antibacterial action against resistant bacteria such as *Mycobacterium avium*, *Mycobacterium intracellulare*, *Mycobacterium tuberculosis,* and *Mycobacterium leprae*. Due to the poor solubility of clofazimine in water, its absorption by the gastrointestinal tract is low, and when administered orally can cause depigmentation in the skin. Poor hydrophobicity of clofazimine allows it to accumulate in the tissues, thus making its elimination difficult from the organism in which its half-life is 70 days. Due to these characteristics, World Health Organization (WHO) recommends clofazimine as a second line of treatment in therapies against drug-resistant tuberculosis [76].

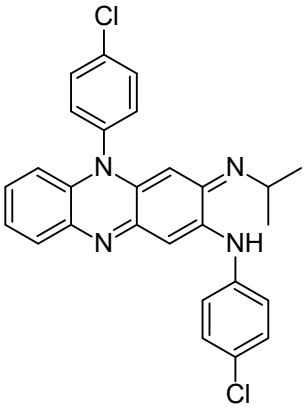


Fig. 5. Chemical structure of clofazimine.

In vitro screening reports carried out with the Food and Drug Administration (FDA) approved drugs showed that clofazimine has antiviral activity [77,78]. Studies were performed on the screening of 1700 drugs against human coronavirus OC43 (HCoV-OC43), and the results indicated that clofazimine has biological activity against HCoV-OC43. These findings motivated the researchers to evaluate clofazimine against the SARS-Cov-2. The experimental results revealed that the clofazimine had EC_{50} >30 μM (CC_{50} = 0.01μM, SI >3000 μM) [78], inhibited viral replication, and showed a very high selectivity index, close to the ideal (SI ≤1).

Another study was executed to assess the antiviral activity of clofazimine via the Vero 6 cell line, and the results showed that clofazimine has an EC_{50} = 310 nM. Although there are reports of the antiviral action of clofazimine against SARS-Cov-2, its mechanism of action has not been discovered so far [79].

High-throughput screening with a library of 1,425 FDA-approved drugs was performed to identify efficient drugs versus SARS-CoV-2. The results also confirmed the dose-responsive antiviral effect of clofazimine versus SARS-CoV-2 in human alveolar epithelial cells with its EC_{50} = 85 nM [80]. Still, there are not many published studies on the antiviral activity of clofazimine versus SARS-CoV-2 available, but there is an ongoing phase 2 clinical trial registered as NCT04465695 with 81 participants [81].

2.5 Azithromycin

A derivative of erythromycin, azithromycin (Fig. 7) was first synthesized in the early 1980s. It is used as an antibiotic and has a wide spectrum of activities including antibacterial activity versus gram-positive and gram-negative bacteria. Azithromycin was first approved in 2007 for ophthalmic use in the treatment of conjunctivitis [82] in addition to treating sexually transmitted infections [83].

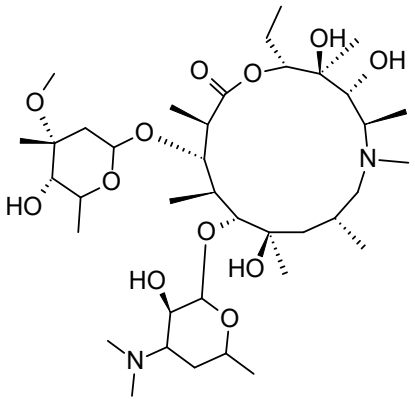


Fig. 6. Chemical structure of azithromycin.

The antiviral activity of azithromycin has already been reported in the literature against rhinoviruses [84,85], zika virus [86], coxsackievirus A16, (CV-A16), enterovirus A71 (EV-A71) [87], and ebola virus [88] through *in vitro* tests. A study published in 2015 reported azithromycin for the treatment of lower respiratory tract illness. The results of the clinical study confirmed the drug's efficiency in the group that received the active principle compared to the group that received a placebo [89]. These findings motivated the researchers to evaluate azithromycin against SARS-Cov-2, and one of the initial studies carried out suggested a synergistic effect between azithromycin and hydroxychloroquine in a clinical investigation conducted on 36 patients [90].

In vitro tests using VeroE6 cells revealed antiviral action of azithromycin versus SARS-Cov-2 with its EC_{50} = 2.12 μM (EC_{90}=8.65 μM, CC_{50}>40 μM, SI>19) [91].

In the clinictrials.gov.br database, there are about 107 registered clinical studies that aim to evaluate the action of this drug against Covid-19, although there are many investigations to evaluate the effect of azithromycin, or of its combination with hydroxychloroquine, statistics indicate that its use as a treatment does not lead to mortality [92,93].

2.6 Apilimod

Apilimod (STA-5326) (Fig. 8) is an investigational drug synthesized by Synta Pharmaceutics Corp. It is an inhibitor of interleukins – a group of cytokines associated with the regulation of immune system response- specifically IL-12 and IL-23. Therefore, the primary idea for its medicinal application

was for the treatment of autoimmune conditions [94]. In an attempt to demonstrate its effectiveness for disorders such as rheumatoid arthritis and Crohn's disease, clinical trials were carried out. The results were unsatisfactory and further attempts to evaluate the efficacy of apilimod were halted [95,96]. Several years later, researchers discovered a new mechanism of action for apilimod that involves the inhibition of a lipid kinase enzyme PIKfyve (Phosphatidylinositol-3-phosphate 5-kinase) [97]. In recent years, apilimod was reconsidered for potential treatments of B-cell non-Hodgkin lymphoma (phase 2), Lassa fever, and Ebola virus [98–100].

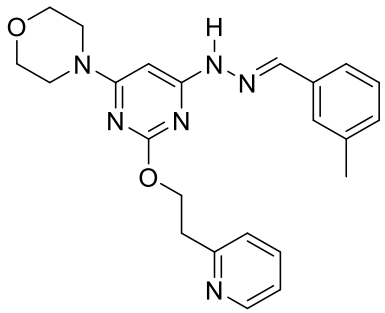


Fig. 8. Chemical structure of apilimod.

Recently, apilimod has grabbed attention as a treatment for the Covid-19. In cells transduced with pseudovirus, drugs penetrate the lysosomes to inhibit the infection. These results suggest that the preferred route for SARS-CoV-2 to access the cell is the endocytic pathway [101]. Since apilimod inhibits PIKfyve enzyme involved in the regulation of endosomal maturation, therefore, it impairs the penetration of pseudovirions SARS-CoV-2 [102,103]. A randomized, double-blind, placebo-controlled trial is being performed to assert the safety and efficiency of apilimod in patients who developed mild symptoms of Covid-19 and currently is in phase 2 (NCT04446377). The trial is expected to be on December 31, 2020 [104].

2.7 Arbidol (Umifenovir)

The synthesis of arbidol (umifenovir) is credited to a group of Russian chemists led by Robert Glushkov 45 years ago. It inhibits the entry of enveloped and nonenveloped viruses such as influenza, parainfluenza, Ebola, hepatitis B, and C to the cells. For this reason, arbidol is considered to be a broad-spectrum antiviral drug [105]. It is used as an antiviral agent for approximately 25 years in Russia and 15 years in China [106]. Reports on arbidol chemical synthesis date back to 1993 [107]. It inhibits entry to the cells by blocking viral fusion with the host cell membrane [108]. In the case of the influenza virus, arbidol increases the stability of hemagglutinin (HA) found on the exterior of the influenza virus, thus prevents HA transition to its fusogenic state, and impairs the low pH-induced conformational changes triggered by ligand binding [105].

Arbidol (Umifenovir) is regarded as a direct-acting antiviral (DAA) agent due to its capability to destroy the virus directly. On the other hand, it also acts as a host-targeting agent (HTA) due to its effects on the viral life cycle such as internalization. It is believed that the efficiency of arbidol against many viruses may be the result of this dual-action [109]. Being a hydrophobic molecule, arbidol can bond with tyrosine or tryptophan by aromatic interactions, leading to stacking of proteins present in virus envelope, this action may explain the drug's ability to act directly against several viruses. The aforementioned interactions of arbidol with aromatic residues within the viral glycoproteins associated with fusion and cellular recognition may also explain its indirect antiviral activity [105,110].

Arbidol belongs to the class of organic compounds known as indolecarboxylic acids and their derivatives. It has a carboxylic acid group linked to an indole group (**Fig. 9**).

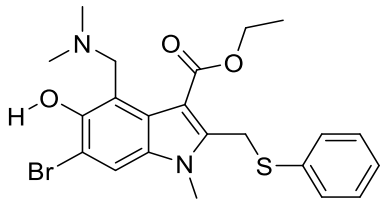


Fig. 9. Chemical structure of arbidol (umifenovir).

Currently, arbidol is being examined as a potential treatment for Covid-19 in association with other drugs. Several clinical trials are being carried out involving arbidol with different outcomes [111–113]. In a preprint report with the participation of 504 Covid-19 patients, the efficiency of arbidol was compared to oseltamivir and lopinavir. Covid-19 patients treated with arbidol showed a decrease in mortality and faster lesion recuperation [114]. In another study administration of arbidol was associated with less viral shedding compared to lopinavir [111]. Yet, in another study, the data suggested better results for arbidol over a combination of lopinavir/ritonavir for the treatment of Covid-19 [115]. Arbidol was associated with a significant reduction of SARS-CoV-2 among health professionals [116]. On the other hand, studies also showed that arbidol did not boost the prognosis or speed up SARS-CoV-2 elimination [112,113]. Although in several studies arbidol demonstrated significant clinical improvement, more trials are still necessary to confirm its efficacy against Covid-19 [4].

2.8 Selinexor

Selinexor (KPT-330) is a fine selective inhibitor of nuclear export (SINE) compound. This drug suppresses exportin-1 (XPO1) by binding to it. Selinexor has demonstrated activity in patients with refractory multiple myeloma, and FDA approved it for the treatment of the disorder in June 2019 [117].

Exportin 1 (XPO1), a nuclear export protein, is overexpressed in multiple myeloma cells, and studies have proposed that XPO1 is vital for the existence of these cells. XPO1 is responsible for the transport of messenger RNA of several oncogenes including cell cycle promoters for example cyclin D1 and cyclin E, as well as antiapoptotic proteins such as Mcl-1 and Bcl-xL [118]. Therefore, the inhibition of XPO1 is crucial to induce tumor cell death. Another study indicates that selinexor acts through NF-κB deactivation, and merge with proteasome inhibitors, leading to apoptosis of tumor cells synergistically [119].

Selinexor is an organic compound with 1,2,4-triazole bonded to a phenyl group, thus it belongs to phenyl-1,2,4-triazoles' class (Fig. 10).

During the pandemic caused by SARS-CoV-2, selinexor caught attention like other investigational SINE as a potential treatment for hospitalized patients with Covid-19. SINE inhibits Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB), a protein complex that regulates

DNA transcription, cytokines generation, and cell viability. Since pulmonary inflammation shows high levels of cytokines, therefore, the suppression of NF-κB by SINE leads to reduction of cytokines production which makes them anti-inflammatory agents [119]. The anti-inflammatory effect could be beneficial to hospitalized patients. A randomized single-blind study is underway to assess the effect and safety of low dose oral selinexor (KPT-330) in patients with severe Covid-19 infection in Phase 2 (NCT04349098).

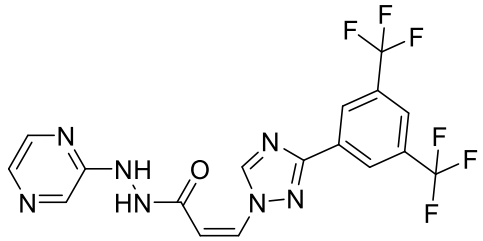


Fig. 10. Chemical structure of Selinexor.

This clinical trial was designed to examine the activity and safety of 20 mg of selinexor administered orally six times in two weeks. Promising results such as a higher percentage of patients discharged after two weeks, higher conversion to negative Covid-19 PCR test, and a reduction in inflammation after eight days of treatment was observed. The trial was carried out with the participation of 66 patients [120].

2.9 Remdesivir

Remdesivir (GS-5734) (Fig. 11) is an investigational new drug created by Gilead Sciences Inc. The research initiated in 2009 to synthesize novel drugs for the treatment of hepatitis C (HCV) and respiratory syncytial virus (RSV) resulted in remdesivir discovery. Remdesivir is an adenosine triphosphate analog that inhibits a reverse transcriptase (RNA polymerase). The drug binds to RNA, impairs other nucleotides before their addition, and consequently causes suppression of the RNA transcription. After confirming that remdesivir showed broad-spectrum antiviral characteristics, it was used for the treatment of Ebola [121]. Moreover, remdesivir has also demonstrated efficacy via '*in vitro*' and '*in vivo*' investigations against RNA virus families, such as *Filoviridae*, *Pneumoviridae*, *Paramixoviridae,* and *Coronaviridae* [122,123].

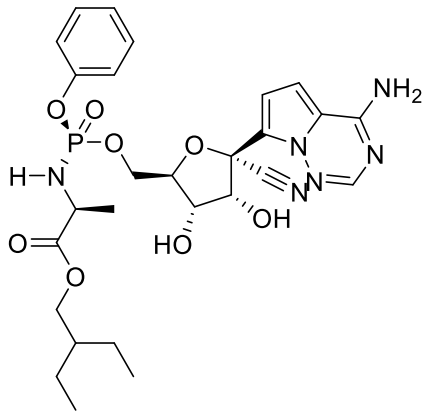


Fig. 11. Chemical structure of remdesivir.

Remdesivir caught attention as the first SARS-CoV-2 patient recovered after treatment with it [124]. Currently, there are 44 trials registered around the world to investigate the efficacy of remdesivir against SARS-CoV-2 infection.

Based on the preliminary data, remdesivir is in the Covid-19 treatment guidelines of the US National Institutes of Health for hospitalized patients who need supplemental oxygen. However, it is not FDA-approved but has been authorized for emergency use. After a positive evaluation of remdesivir, the CHMP (Committee on Human Medicinal Products) granted a conditional authorization of its use in Europe, where it is presently recommended for the treatment of Covid-19 patients of age group older than 11 years, and with a body weight of over 40 kg who developed pneumonia and need supplemental oxygen.

WHO solidarity trial is one of the world's largest trials for Covid-19 therapies. The interim results of the trial indicated that none of the four antiviral drugs tested on 11,000 patients in 400 hospitals around the world increased survival. The four drugs studied were: i) hydroxychloroquine, ii) combination of ritonavir/lopinavir, iii) remdesivir and iv) interferon β [125]. Though the results of another trial carried out on more than 1000 Covid-19 patients in the US indicated a shorter recovery time for patients who used remdesivir as compared to the control group. However, no substantial difference in mortality was observed [126].

2.10 Methylprednisolone

Methylprednisolone (Fig. 12) belongs to the class of glucocorticoids (involved in glucose metabolism) and was first reported in the late 1950s [127,128]. It was approved by FDA as an anti-inflammatory drug in 1957.

Methylprednisolone, like other glucocorticoids, inhibits the initial events in the inflammatory response including the inhibition of vasodilation and the vascular permeability diminishing leukocyte migration to the inflammatory site. Furthermore, it also inhibits NF-κB and other inflammatory transcription factors. This mechanism leads to a decrease in inflammation and the suppression of the immune system. Methylprednisolone is recommended in many conditions including rheumatic disorders, allergies, asthma, certain cancers, multiple sclerosis [129].

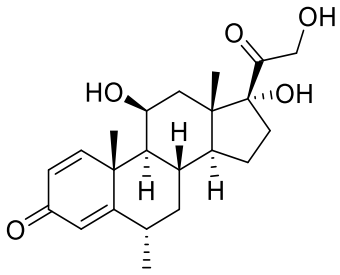


Fig. 12. Chemical structure of methylprednisolone.

During the outbreak of the current coronavirus pandemic, low-dose methylprednisolone-based therapy was successful in treating Covid-19-associated pneumonia in one patient with long-term immunosuppression [130].

The efficacy of methylprednisolone in novel coronavirus pneumonia is being investigated further via more than 50 clinical trials. A Meta-analysis performed by the WHO Rapid Evidence Appraisal for Covid-19 Therapies (REACT) Working Group was published on October 6, 2020. The analysis concluded that the administration of systemic corticosteroids to severe Covid-19 patients, together with usual care or

placebo resulted in lower overall mortality. This potential meta-analysis included seven clinical trials from around the world (NCT04325061, NCT04327401, NCT04381936, NCT02517489, NCT04348305, NCT02735707, and NCT04244591) [131].

2.11 Camostat mesylate

Camostat (trade name FOIPAN® - Fig. 13), was introduced in Japan as a synthetic serine protease suppressant in the 1980s. The drug was marketed in January 2006 to control diseases such as chronic pancreatitis, reflux, and postoperative esophagitis [132]. Camostat mesylate is orally bioavailable and is known for its anti-inflammatory, antifibrotic and antiviral properties [133].

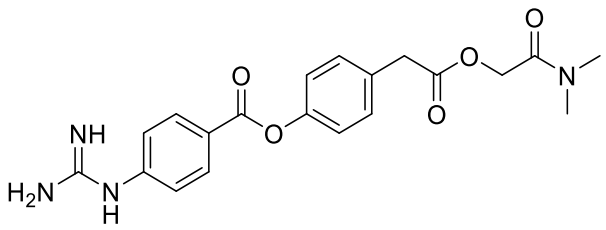


Fig. 13. Chemical Structure of camostat.

After administration, the camostat ion and its metabolite 4- phenyl acetic acid (FOY 251) interrupt the activities of some substances such as trypsin, kallikrein, thrombin, and plasmin, and C1r- and C1 esterases [134]. Importantly, camostat inhibits the activity of serine 2, which mediates entry of influenza and corona viruses into the cells, thus inhibiting infection of the two viruses and their multiplication [135].

Recent studies indicate that the SARS-CoV-2 apex proteins link to the ACE-2 receptor to enter the host cell, and also bind to the transmembrane serine protease 2 (TMPRSS2) (predominantly present in pulmonary epithelial cells) to target host cells [134].

Since the mechanism of action of camostat mesylate involves the blocking of TMPRSS2, therefore, it might be useful to combat COVID-19 as well. Research has shown that interference in the entry of the corona virus into cells leads to the inhibition of host protease (TMPRSS2) necessary for the proteolytic processing of protein S of the corona virus [136].

2.12 Aplidin

Aplidin or plitidepsin (Fig. 14) is an antitumor, antiviral, and immunosuppressant medication. It has been reported to cause shrinkage of tumors in the pancreas, stomach, bladder, and prostate [137].

Research studies revealed that several natural products from marine plants and animals contain antitumor agents. The antimitotic properties of marine compounds are responsible for their antitumor nature. Aplidin is also obtained from the marine macroorganism *Aplidium albicans*. Research studies have revealed that aplidin in controlled concentrations exhibits potent anticancer activity against several human myeloma cell lines including those resistant to new anti-myeloma agents [138].

In March 2020, pharmaceutical company PharmaMar reported that aplidine also has antiviral activity. Research has shown that aplidine interferes with Elongation factor 1-alpha (EF1A), which is the focal point for the multiplication and dissemination of the coronavirus. The antiviral activity of aplidine was first examined in a human blood cell line infected with the HCoV-229E-GFP, a virus similar to SARS-CoV-2. The initial results were considered positive, and a clinical trial with a randomized concept (Phase 1) is underway (NCT04382066) [139].

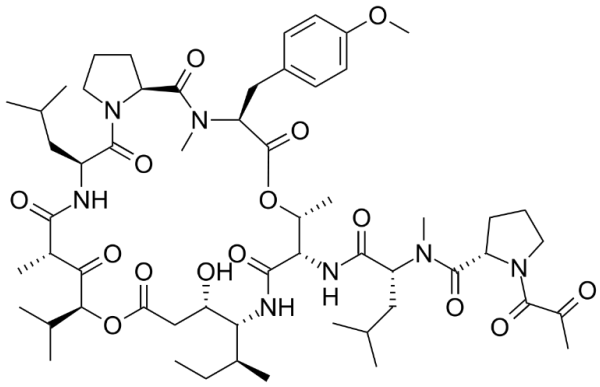


Fig. 14. Chemical structure of aplidin.

The so-called research: "Proof-of-concept study to assess the safety profile of plitidepsin in patients with COVID-19 (APLICOV-PC)" has been developed by the pharmaceutical company "PharmaMar" responsible for the commercialization of the drug [140].

At the beginning of the pandemic, the number of patients with pneumonia increased rapidly and no specific antivirals drugs were available to treat Covid-19. Under the circumstances, aplidin was tested due to its ease of availability, and it showed antiviral activities in hospitalized Covid-19 patients [140].

In vitro investigations indicated that aplidin targets eukaryotic translation elongation factor 1 alpha 1 (EF1A) which are crucial to the growth of the virus. The antiviral effect of aplidin was primarily evaluated in a human hepatoma cell line infected with the HCoV-229E-GFP virus, which is similar to SARS-CoV-2. The initial results are encouraging, but a randomized, multi-centered proof of concept (Phase 1) clinical trial is in progress and patients are presently being tested (NCT04382066) [141].

The main treatment goal was the selection of the recommended dose levels of aplidin for Covid-19 patients. Additionally, these tests aim to evaluate the safety, toxicity profile, and primary efficacy of aplidin at each dose administered to hospitalized Covid-19 patients [140].

2.13 Captopril

Captopril (Fig. 15) was discovered in the 1960s by a Brazilian physician and pharmacologist Sérgio Henrique Ferreira and is used for the treatment of hypertension. According to Biyani, et al., captopril is an angiotensin-converting enzyme (ACE) inhibitor in the market, which presents a high dissolution content, avoids the formation of stones, improves blood pressure, protects kidney function, and can be used in patients with different comorbidities. However, the authors report the use of captopril (as well as other ACE inhibitors) to be controversial since they may worsen the symptoms in Covid-19 patients. Captopril efficacy against Covid-19 is still being investigated, whereas patients with comorbidities such as hypertension and diabetes are encouraged to continue its use [142].

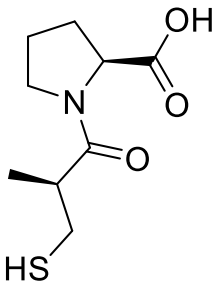


Fig. 15. Chemical structure of captopril.

Captopril is an effective drug available in liquid form. According to the pharmaceutical company responsible for the commercialization of captopril, it should be administered by nebulization to potentiate the pulmonary action and minimize its side effects. Severe Covid-19 has been reported to cause pneumonia which can then lead to acute respiratory distress syndrome (ARDS), the principal cause of death from SARS-Cov-2 with a mortality rate of 3%.

According to FDA research, SARS-Cov-2 uses angiotensin 2 to produce its peak ECA2 protein in the alveoli. The angiotensin-converting enzymes ACE and ACE2 are present in the respiratory epithelium and have opposite functions. These two enzymes have negative control of each other, one inhibiting the other. SARS-Cov-2 negatively regulates ACE2 by using it as a cell receptor, regulating it downwards, whereas the ACE is upregulated causing further damage to the alveoli, and aggravation of acute respiratory failure. Captopril is an ACE inhibitor commonly used to treat hypertension worldwide. However, its use for the treatment of Covid-19 can be counterintuitive. During clinical trials, 25 mg of captopril was administered to the hospitalized Covid-19 patients. Although controversial, it seems that ACE2 protects against lung injury, which could lead to a positive outlook for Covid-19 treatment [143].

Some research studies have shown satisfactory results, stating that the use of captopril is the simplest way to increase ACE2 in pneumonia patients caused by SARS-Cov-2. Studies revealed that 10 to 19 percent of the Covid-19 patients hospitalized in China were diabetic. These findings encouraged the researchers to begin the investigations with the captopril medication. Studies revealed that captopril had a statically more relevant Antibody-dependent enhancement (ADE) response when compared to other ACE inhibitors (P = 0.005), as well as angiotensin II receptor blockers (ARBs) (P = 0.012), although some other specific drugs also have important pulmonary ADEs response related to their usage. These studies indicate that both doctors and pharmacists will need to take into account the adverse effects of captopril, as it can lead to infections and other acute diseases that affect the functioning of the lungs [144].

During studies on patients with high blood pressure, the amount of angiotensin did not appear to be affected after the first treatment with the ACE inhibitor captopril. However, the level of angiotensin increased with monotherapy for 6 months. These findings suggest that the effects of ACE 2 should not be extended to all the renin-angiotensin-aldosterone system (RAAS) inhibitors equally. It is imperative to note that the plasma level of ACE 2 may not be a reliable indicator [145].

There are several studies on the drug captopril associated with high blood pressure, and its complications, such as stroke and kidney problems. This ACE enzyme inhibitor is also being tested for the treatment of Covid-19 [142].

2.14 Valsartan

Valsartan (Fig. 16) was discovered in 1989 and is used for the treatment of heart failure, high blood pressure, and post-myocardial infarction. It was reported that the treatment of patients with valsartan decreases their risk of heart attacks and stroke. The drug is also used for the treatment of other disorders such as shortness of breath and swelling of the feet and legs due to heart failure. For people who have suffered a heart attack, valsartan is reported to enhance their survival chances by reducing heart problems [146].

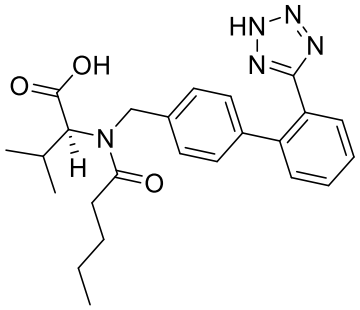


Fig. 16. Chemical structure of valsartan.

A hypothesis is being investigated, which states that another drug sacubitril acts by inhibiting neprilisin when combined with valsartan in the advanced stages of Covid-19 patients. Combating the current pandemic is a tough task that presents several challenges. One of the strategies to overcome the Covid-19 pandemic is through the use of existing therapeutic approaches. It was reported that the combined use of sacubitril and valsartan not only increased the therapeutic efficacy against cardiovascular disorders but also demonstrated promising results to reduce the risk of infection and complications in Covid-19 patients. There is also evidence of a significant increase in the N-terminal prohormone of brain natriuretic peptide (NT-proBNP) in Covid-19 patients. Thus, it is believed that the use of sacubitril + valsartan can be efficient in the most severe stages of Covid-19 infection, with anti-inflammatory and antifibrotic effects of the two drugs [147].

The latest research has shown that combined use of sacubitril and valsartan decreased the concentration of pro-inflammatory cytokines and the number of neutrophils, whereas increased the lymphocyte count more than valsartan alone or placebo. Furthermore, the results suggested that early administration of sacubitril + valsartan reduces the amount of highly sensitive C-reactive protein and increases the number of lymphocytes in patients with acute heart failure. Overall, the data indicated that early administration of sacubitril + valsartan to Covid-19 patients is positive to enhance the anti-inflammatory effects of sacubitril and contain the effect of angiotensin I in the lungs [148].

Valsartan belongs to a class of drugs known as angiotensin II receptor antagonists, which act by controlling high blood pressure. Angiotensin II causes blood vessels to contract, leading to increased blood pressure. Thus, valsartan acts as a regulator of the effect of angiotensin II, resulting in the relaxation of the veins, consequently reducing the blood pressure [146].

In hospitalized patients with symptoms of corona virus, a positive activity of the valsartan was observed. Clinical results demonstrated that the use of valsartan could be an alternative to treat Covid-19 patients. SARS-CoV-2 has a high mortality

and morbidity rate due to the development of Acute Respiratory Discomfort Syndrome (ARDS). The renin-angiotensin system (SARS) plays a vital role in the development of ARDS. The SARS Cov-19 virus protein binds to ACE2, forming a complex suitable for cell internalization. The negative regulation of ACE2 leads to excessive accumulation of angiotensin II, and it was observed that the stimulation of this receptor (angiotensin II type 1a (AT1R)) causes an increase in pulmonary vascular permeability, which explains the increase in pulmonary pathology when ACE2 activity is reduced. The available AT1R blockers (BRAs), (such as valsartan) suppress this pathological process mediated by angiotensin II [149].

2.15 Verapamil

Verapamil (Fig. 17) is used for the treatment of ischemia (lack of oxygen to the heart muscle) with or without angina, mild and moderate arterial hypertension, and the prevention of arrhythmia. It can be used by patients with other comorbidities such as diabetes, asthma, depression, sexual impotency, with no contraindications for elderly patients. This substance works by blocking the flow of calcium to the arterial and vascular cardiac muscle cells, improving the amount of oxygen to the heart (slow channel blocker or calcium ions antagonist) [150].

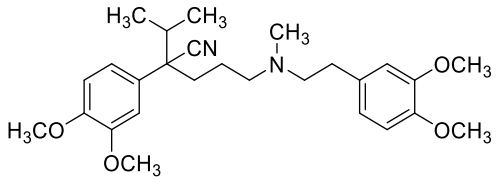


Fig. 17. Chemical structure of verapamil.

Currently, verapamil is prescribed for frequency control in supraventricular tachycardia, and treatment for high blood pressure and migraine. Recent research is focused on the possibility that this drug is suitable for the treatment of high blood pressure in Covid-19 patients. Preliminary animal data demonstrate that verapamil has no effect on the expression of ACE2, and that it improves the clinical and pathological picture of viral myocarditis. The cardiac effects and especially myocarditis associated with SARS-CoV-2, represent a serious and fatal effect of Covid-19. Therefore, the treatment of high blood pressure through a drug that can reduce inflammation in viral myocarditis and does not have a risk of promoting the proliferation of Covid-19 seems to be a good strategy to optimize the results for the treatment purpose. Moreover, Covid-19 patients with the complication of high blood pressure are likely to improve with verapamil or carvedilol since these agents control blood pressure and can mitigate inflammation and necrosis in SARS-myocarditis [151].

Studies have further shown that amiodarone or verapamil can interfere with coronavirus entry and severity by blocking ion channels. Some studies show that comorbidities damage the vascular system, and the patients may have severe vascular symptoms with a systemic response when infected with Covid-19, leading to worsening of the disease faster. These patients may have refractory epileptic seizures, that respond poorly to other antispasmodics. Furthermore, it is expected that the use of verapamil caused a rapid and satisfactory response in the recovery of these specific patients. With the urgent need to identify stable and effective therapeutic options against early stages of viral infection and replication, research with the ion channel inhibitors of the cardiovascular system: amiodarone and verapamil, and their possibility to reduce disease severity and transmission, is bringing a very promising aspect to the studies. Since the modulation of the cell's ion channel activity host, by viral proteins, is being increasingly identified as an important virus-host interaction [152].

Verapamil selectively inhibits the flow of intracellular Ca^{2+} transmembrane through the L-type voltage-dependent Ca^{2+} channels. Data from *in vitro* experiments showed that amiodarone and verapamil in human serum can act as targeting agents for the host cell that blocks the entry of the filovirus. These results confirm that Ca^{2+} channel activity is necessary during the entry of the Sar-Cov-2 virus. The goal is to treat hospitalized Covid-19 patients. Initially, the dose is given intravenously, whereas the remaining doses are administered orally followed by the first intervention, with clinical improvement being observed between the first and seventh days after the beginning of the treatment with verapamil [153,154].

2.16 Lopinavir/Ritonavir

Lopinavir/Ritonavir (Fig. 18), formerly known as ABT-378/R, are viral inhibitors of protease synthesis. The two drugs were approved for clinical use by the FDA on September 15, 2000, under the trade name KALETRA, and are initially manufactured by Abbott laboratories [155].

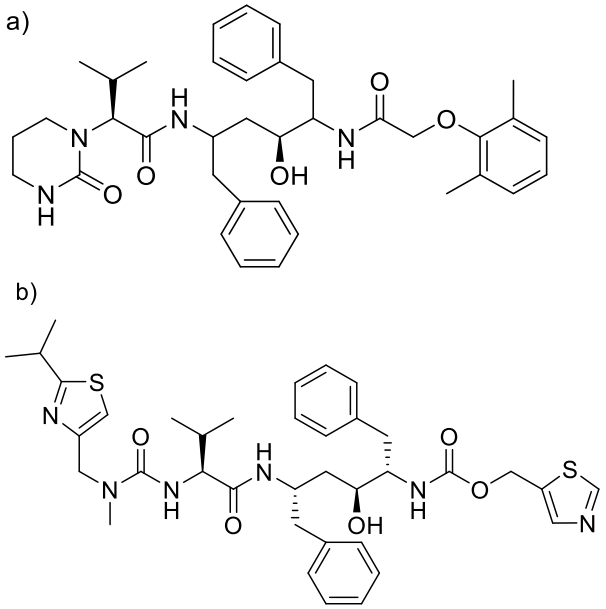


Fig. 18. Chemical Structure of lopinavir (a) and ritonavir (b).

The two drugs work by inhibiting the activity of the protease enzyme, prevent the cleavage of polyproteins and cause the production of immature and non-infectious viral particles [156]. The combination of the two drugs is well tolerated with diarrhea, nausea, and gastrointestinal adverse events, with abnormal bowel movements being their most common adverse events. Laboratory abnormalities are usually regarded as enhancements in cholesterol and triglyceride levels [157].

The combination of lopinavir and ritonavir tends to increase plasma lopinavir levels (since lopinavir metabolism is inhibited), reaching higher viable levels to inhibit viral protease [156,157].

Ritonavir is a peptidomimetic hydroxyethyl amine, which acts as a human immunodeficiency viruses (HIV) protease inhibitor [158]. The mechanism of action involves reversible binding of ritonavir to the active site of HIV protease, thus preventing the polypeptide from processing and the subsequent maturation of the virus. According to Molla et al., the viral particles generated in the presence of ritonavir are immature and non-infectious [158]. This drug was the first to inhibit the HIV protease to enhance patients' survival [159].

Adverse effects of ritonavir depend on the quantity of dose administered, and consist of gastrointestinal symptoms such as diarrhea, nausea, abdominal pain, anorexia, and dysgeusia (distortion of the sense of taste). Peripheral and perioral paresthesia can usually occur as well [160].

Lopinavir has been reported to exhibit antiviral activity against Middle East respiratory syndrome coronavirus (MERS-CoV) in Vero cells, with its half-maximal inhibitory concentration (IC_{50} value) of 8 μM. Since lopinavir is a protease inhibitor, therefore, its combined use with ritonavir has the potential to treat COVID-19 [7,115,161–163]. In another study, lopinavir suppressed SARS-CoV-2 reproduction in Vero E6 cells with its IC_{50} value of 26.63 μM [65]. In an *in silico* study lopinavir/ritonavir demonstrated inhibition against SARS-CoV-2 main protease (M^{PRO}) [164]. The combination of lopinavir/ritonavir has been previously studied via *in vitro* and clinical trials, where it has shown antiviral effects against SARS-CoV [165]. However, the combination of the two drugs is applied in several countries for emergency treatment of COVID-19 [7,166,167].

2.17 Interferon Beta

Interferon-beta (Fig. 19) belongs to the interferon family and is commonly used for the treatment of multiple sclerosis.

This drug has two formulations available: interferon beta-1a (Avonex [Biogen Idec; Cambridge, MA] and Rebif [EMD Serono; Rockland, MA]), which is almost similar to natural interferon–beta and interferon beta-1b (commercially known as Betaferon/Betaseron [Bayer HealthCare Pharmaceuticals; Whippany, NJ] and Extavia [Novartis Pharmaceuticals Corporation, East Hanover, NJ]) [168]. This drug is used for the treatment of recurrent-remitting multiple sclerosis, secondary progressive multiple sclerosis with active disease, and Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [169,170].

Although the exact mechanism of action of the Interferon-beta-1-b and its effects are still unknown, it has been reported to possess immunomodulatory and anti-inflammatory effects, such as decreasing the activity of the T lymphocyte cytosine Th1 subset by inducing the production of IL-10. The interferon beta also decreases the production of pro-inflammatory cytokine IL-17, causing a reduction in the proliferation of T lymphocytes and the presentation of antigens. It causes also, a reduction in the permeability of the blood-brain barrier when interrupting adhesive interactions, reducing the effect of matrix metalloproteinases and leukocyte migration [171–175].

During the MERS and SARS outbreaks, interferon-beta showed *in vitro* antiviral effects against the two viral strains. Therefore, it was used for the treatment of the complications related to the two viruses [176–178]. Another study indicated the potential efficacy of human type I interferons (IFNs) in suppressing SARS-CoV-2 infection. The half-maximal effective concentration (EC_{50} values) of IFN-α and IFN-β treatment was reported to be 1.35 IU/mL and 0.76 IU/mL, respectively, in Vero cells. These findings provided a piece of evidence for the potential use of interferon family as a treatment against Covid-19 [178,179]. According to the platform clinicaltrials.gov (NCT04350684), the efficacy of interferon-beta combined with other drugs for the treatment of Covid-19 patients has already reached stage IV during clinical trials [180,181].

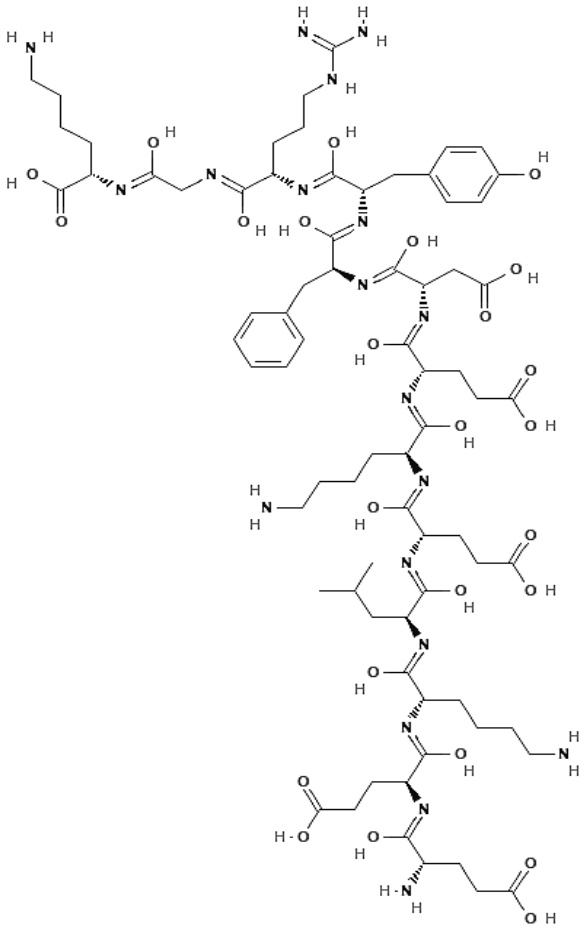


Fig. 19. Chemical Structure of Interferon-beta.

2.18 Ribavirin

Ribavirin is a nucleoside analog drug of guanosine, which can be easily confused with other purines. It is commonly used to treat numerous viral complications such as respiratory syncytial virus (RSV) infection, chronic hepatitis C, and several viral hemorrhagic fevers. This drug (Fig. 20) was synthesized for the first time in the 1970s by researchers at ICN Pharmaceuticals (Valeant International Pharmaceuticals) [181–184].

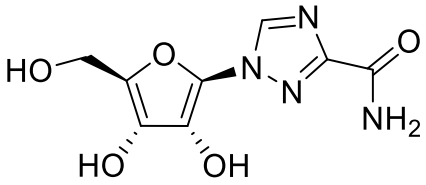


Fig. 20. Chemical structure of ribavirin.

Ribavirin has some proposed mechanism of action more explored is the mechanism of its monophosphate. Inhibition of the inosine monophosphate dehydrogenase causes a

decrease in the intracellular concentration of GTP. Upon incorporation into viral RNA, ribavirin inhibits the synthesis of viral RNA, which consequently inhibits their replication [185,186].

Besides, ribavirin caused inhibition of SARS-CoV replication tested in five different types of cells derived from animals and humans [186,187]. It can also be used in combination with interferon-alpha or lopinavir/ritonavir [188]. However, there are some *in vivo* studies that indicate that ribavirin did not inhibit the replication of SARS-CoV, and was, therefore, found unsuitable for the treatment of SARS infections [189,190]. Still, ribavirin requires further studies to prove its efficacy against Covid-19.

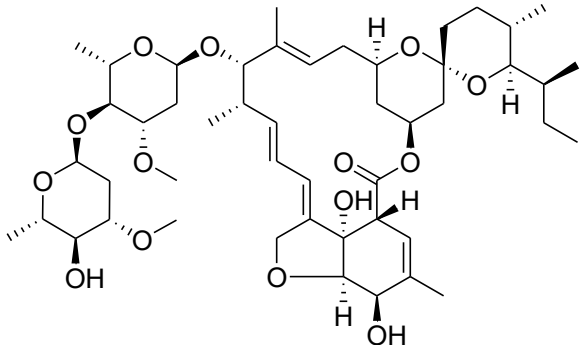


Fig. 21. Chemical structure of ivermectin.

2.19 Ivermectin

Ivermectin (Fig. 21) is a macrocyclic lactone from the bacterium *Streptomyces avermitilis* and was discovered by Professor Satoshi Ōmura in 1975. It is a broad-spectrum medication used to treat several parasite infestations such as scabies, onchocerciasis, and nematodes [191,192]. Ivermectin is being marketed on large scale since 1981 due to its high efficacy and low cost. Moreover, it is also included in the WHO twenty-first list of essential products [193].

Besides, unique antiparasitic characteristics of ivermectin, it is a versatile drug for the treatment of bacterial infections [194,195], and some chronic pathologies [196]. Some studies have also confirmed antiviral and anticancer activities of ivermectin [197,198]. Numerous *in vitro* and *in vivo* investigations indicated that ivermectin had promising antiviral activities against some types of viruses [192].

The proposed mechanism of action revealed that ivermectin works through the inhibition of nuclear transport mediated by the heterodimer α/β1 of the importin, responsible for the translocation of several species of viral proteins (HIV-1, SV40), vital for their replication [181,192,199,200]. This mechanism of action was evaluated through *in vitro* and *in vivo* studies, and the results showed that the inhibition can affect some RNA viruses [192,201,202] such as the Venezuelan equine encephalitis virus [192,203], the dengue virus [192,204], Influenza virus [192,205], the West Nile virus [192,206], and the pseudo-rabies virus (DNA-based genome) [192,207].

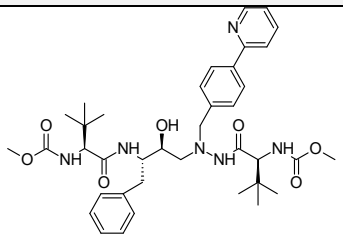
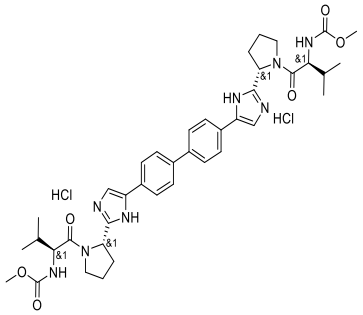
A recent *in vitro* study revealed that ivermectin inhibits the replication of the SARS-CoV-2 virus, however, its mechanism of action was not clear [192,202]. Knowing that the causative agent of COVID-19 is an RNA virus, we can assume interference with similar proteins and, the same molecular phenomena already shown above. This drug can act as a powerful antiviral agent and can be used for possible treatment of the new coronavirus. A possible interaction mechanism involves a reaction between two ivermectin molecules in a "head-tail" fashion to form a complex.

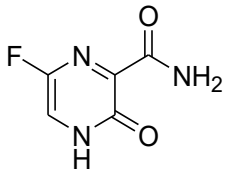
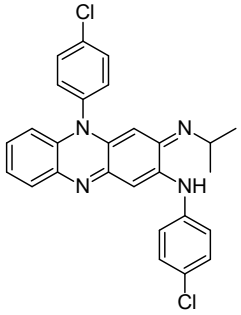
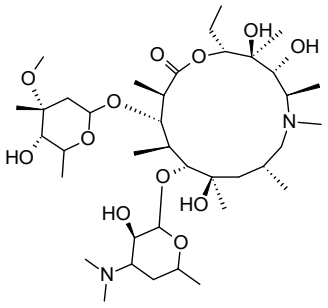
This interaction can happen impulsively or be facilitated by binding through some proteins plasma transport, especially, albumin [192,208].

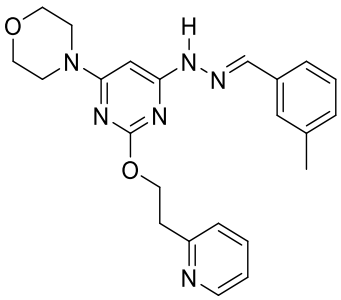
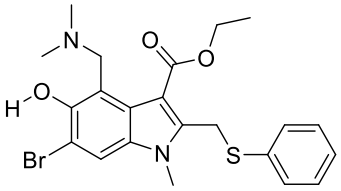
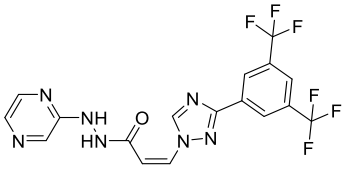
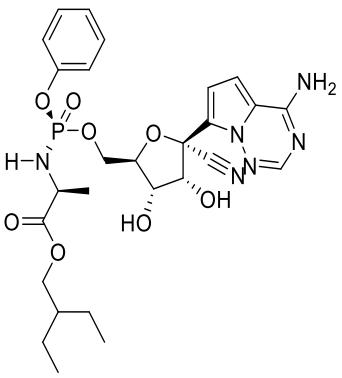
However, this interaction can neutralize the virus in the preliminary stage of the infection adhering to the host cells before entering to initiate the production of other viral particles. However, this phenomenon would work only against viruses without a protein capsid (structure resistant to osmotic pressure) even if to a smaller degree than a fungal, bacterial, or plant cell wall [192,209].

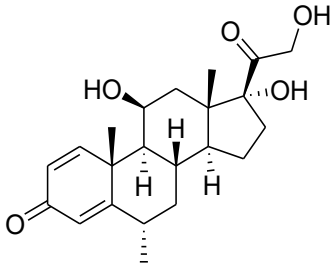
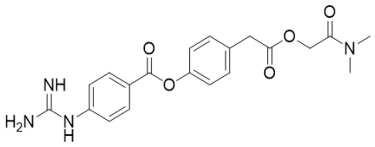
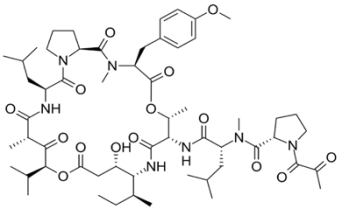
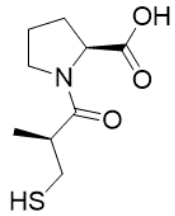
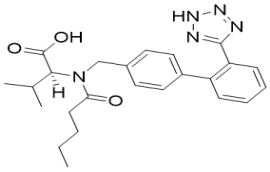
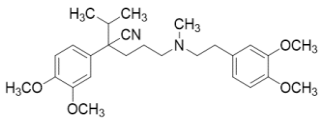
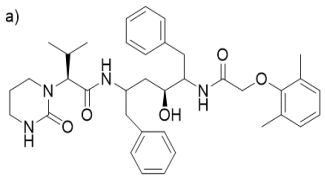
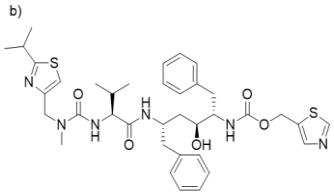
Another study also revealed that ivermectin shows inhibitory effects versus SARS-CoV-2 *in vitro*. The results showed that ivermectin reduced viral RNA up to 5,000 times in Vero-hSLAM cells after 48 hours of SARS-CoV-2 infection. However, further research studies are needed for the possible treatment of Covid-19 patients through ivermectin [210]. Other studies in progress related to compounds (**1-19**) are listed in Table 4.

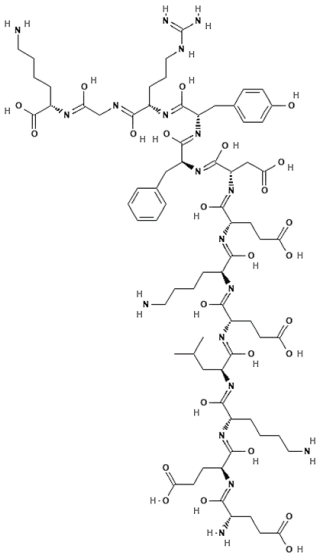
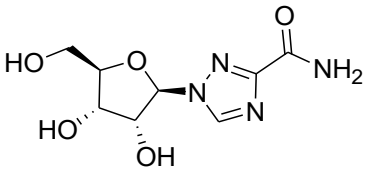
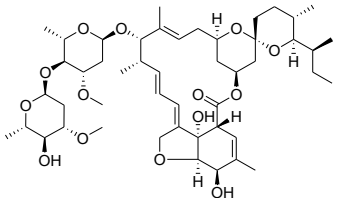
Table 4. Clinical studies registered in the clinicaltrials.gov database for compounds **(1-19)**.

Compound	Chemical structure	Registration ID	Phase	Ref.
1. Atazanavir		NCT04459286	II	[211]
		NCT04452565, NCT04468087	III	
2. Daclatasvir		NCT04561063, NCT04532931	II	[212]
		NCT04535869, NCT04443725, NCT04497649, NCT04468087, NCT04460443	III	

		NCT04444986, NCT04406194, NCT04400682, NCT04407000	I	
		NCT04358549, NCT04448119, NCT04475991, NCT04346628, NCT04387760, NCT04445467, NCT04499677, NCT04532931, NCT04403477, NCT04405310.	II	
3. Favipiravir		NCT04336904, NCT04558463, NCT04464408, NCT04529499, NCT04434248, NCT04425460, NCT04349241, NCT04542694, NCT04402203, NCT04351295, NCT04411433, NCT04303299, NCT04373733, NCT04501783, NCT04361461.	III	[213]
		NCT04359615	IV	
		NCT04474457, NCT04392973, NCT04376814, NCT04310228, NCT04333589, NCT04527133, NCT04542941	Not Applicable	
4. Clofazimine		NCT04465695	II	[81]
		NCT04348474, NCT04329572	Early phase I	
		NCT04343092, NCT04344457, NCT04590274, NCT04457609, NCT04461925, NCT04333355, NCT04390152, NCT04595136, NCT04591600	I	
		NCT04329832, NCT04339426, NCT04336332, NCT04358068, NCT04332094, NCT04501965, NCT04341207, NCT04575558, NCT04335552, NCT04458948, NCT04392128, NCT04374552, NCT04369365, NCT04395768, NCT04341870, NCT04322396, NCT04344457, NCT04334512, NCT04345861, NCT04459702, NCT04502342, NCT04366089, NCT04354428, NCT04390152, NCT04381936, NCT04461925, NCT04374019, NCT04398004, NCT04386447, NCT04359095, NCT04347031, NCT04350281, NCT04401475, NCT04395170, NCT04608214, NCT04360980, NCT04595136, NCT04349410, NCT04591600, NCT04374539, NCT04405310	II	
5. Azithromycin		NCT04381962, NCT04334382, NCT04363060, NCT04332107, NCT04359953, NCT04365231, NCT04358081, NCT04405921, NCT04371406, NCT04347512, NCT04339816, NCT04371107, NCT04530422, NCT04363203, NCT04328272, NCT04355052, NCT04344379, NCT04344444, NCT04341870, NCT04341870, NCT04338698, NCT04613271, NCT04361461, NCT04321278, NCT04382846, NCT04322123, NCT04528927, NCT04383717, NCT04345861, NCT04345861, NCT04365582, NCT04411433,	III	[214]

		NCT04341727, NCT04323345, NCT04354428, NCT04354428, NCT04342221, NCT04381936, NCT04381936, NCT04390594, NCT04359095, NCT04359095, NCT04558463, NCT04361422, NCT04401475, NCT04401475, NCT04347031, NCT04347031, NCT04395170, NCT04395170, NCT04542694, NCT04353180, NCT04349410, NCT04349410, NCT04346693, NCT03871491 NCT04359316, NCT04370782, NCT04621461, NCT04351919, NCT04394377, NCT02735707 NCT04374903, NCT04622891, NCT04349592, NCT04354597, NCT04399746, NCT04441424, NCT04476888, NCT04446429, NCT04463420, NCT04348877, NCT04492501, NCT04388514, NCT04403646, NCT04380818, NCT04394182	IV Not Applicable	
6. Apilimod		NCT04446377	II	[215]
7. Arbidol (Umifenovir)		NCT04476719, NCT04323345, NCT04501783 NCT04350684, NCT04286503, NCT04260594 NCT04273763, NCT04261907, NCT04333589 NCT04355676, NCT04349098	I III IV Not Applicable II	[216]
8. Selinexor		NCT04534725	III	[217]
9. Remdesivir		NCT04560231 NCT04539262, NCT04482699, NCT04536350, NCT04429529, NCT04480333, NCT04401410, NCT04335123 NCT04431453, NCT04410354, NCT04539262, NCT04330690, NCT04583956, NCT04583969, NCT04345419, NCT04575064, NCT04488081, NCT04321616, NCT04519424, NCT04373044, NCT04359095, NCT04482699, NCT04401475, NCT04359901, NCT04386447, NCT04395170, NCT04403477, NCT04345614, NCT04405310, NCT04349410, NCT04334460, NCT04610138 NCT04431453, NCT04292899, NCT04292730, NCT04252664, NCT04501952, NCT04409262, NCT04257656, NCT04610541, NCT04401579, NCT04492475, NCT04280705, NCT04345419, NCT04575064, NCT04593940, NCT04321616, NCT04315948, NCT04546581, NCT04501978,	Early phase I I II III	[218]

		NCT04370262, NCT04359095, NCT04401475, NCT04523831, NCT04395170, NCT04361461, NCT04349410		
10. Methyprednisolone		NCT04374071	-	[219]
11. Camostat		NCT04435015, NCT04321096	I and II	[220]
		NCT04583592, NCT04353284, NCT04524663, NCT04530617, NCT04470544, NCT04374019, NCT04521296	II	
		NCT04455815	II and III	
		NCT04355052	III	
		NCT04338906	IV	
12. Aplidin		NCT04382066	I	[221]
13. Captopril		NCT04578236, NCT04355429	II	[143]
		NCT04345406	III	
		NCT04330300	IV	
		NCT04467931	Not Applicable	
14. Valsartan		NCT04591210	III	[222]
		NCT04335786, NCT04330300, NCT04394117	IV	
		NCT04467931	Not Applicable	
15. Verapamil		NCT04351763	II	[150]
		NCT04330300	IV	
		NCT04467931	Not Applicable	
16. Lopinavir (a)/ Ritonavir (b)	 	NCT04382950, NCT04335123, NCT04386876	I	[223]
		NCT04390152	I and II	
		NCT04307693, NCT04372628, NCT04499677, NCT04455958, NCT04330690, NCT04346147, NCT04521400, NCT04343768, NCT04459702, NCT04276688, NCT04373044, NCT04387760, NCT04386447, NCT04393051, NCT04366089, NCT04350281, NCT04360980, NCT04329650, NCT04389580, NCT04374539, NCT04403477	II	
		NCT04466241, NCT04328012, NCT04331470, NCT04358614, NCT04354428, NCT04351724,	II and III	

		NCT04434248, NCT04320277, NCT04381936, NCT04401475, NCT04359095, NCT04402203, NCT04418128, NCT04410510 NCT04409483, NCT04328285, NCT04403100, NCT04321174, NCT04364022, NCT04386070, NCT04365582, NCT04483960, NCT04315948, NCT04361422, NCT04542694, NCT04323345, NCT04523831, NCT04328480, NCT04353180, NCT04350320, NCT04303299	III	
		NCT04255017, NCT04286503, NCT04350684, NCT04350671, NCT02735707	IV	
		NCT04376814, NCT04261907, NCT04295551, NCT04251871, NCT04388514, NCT04380818, NCT04394182, NCT04373824, NCT04542941, NCT04403646, NCT04333589	Not Applicable	
		NCT04465695, NCT04343768, NCT04494399, NCT04330690, NCT04521400, NCT04449380, NCT04350281	II	
		NCT04492475	III	
17. Interferon Beta				[224]
		NCT04350671, NCT04350684	IV	
		NCT04356677, NCT04494399, NCT04374071, NCT04335123	I	
		NCT04551768, NCT04563208, NCT04276688	II	
18. Ribavirin		NCT04392427, NCT04402203	II and III	[225]
		NCT04460443	III	
		NCT04293887, NCT04306497, NCT04278404	Not Applicable	
		NCT04343092	I	
		NCT04472585	I and II	
		NCT04381884, NCT04390022, NCT04510233, NCT04438850, NCT04407507, NCT04551755, NCT04407130, NCT04447235, NCT04431466, NCT04374019, NCT04482686	II	
19. Ivermectin		NCT04360356, NCT04445311, NCT04351347, NCT04403555, NCT04529525, NCT04422561, NCT04405843	II and III	[226]
		NCT04523831, NCT04530474, NCT04527211, NCT04391127, NCT04392427, NCT04382846, NCT04446104	III	

NCT04435587	IV
NCT04425707, NCT04392713, NCT04373824, NCT04429711, NCT04399746, NCT04434144, NCT04425863, NCT04425850, NCT04384458, NCT04446429, NCT04460547	Not Applicable

3. Conclusions

SARS-CoV-2 originated in China in December 2019 and quickly turned into a pandemic with approximately 93 million recorded Covid-19 cases and more than 2 million deaths recorded till January 18th, 2021, worldwide (data from Johns Hopkins University). Due to the fatal nature of Covid-19, swift treatment is needed. Therefore, several FDA-approved/repurposed drugs were recommended as antiviral agents to treat Covid-19 patients in clinics. Several antiviral drugs have exhibited potential efficacy against SARS-CoV-2. This review highlights nineteen key FDA-approved drugs that have exhibited antiviral activities against SARS-CoV-2. However, all the drugs (listed in this study) still require further assessment through prompt preclinical animal investigations as well as clinical trials to find out their real efficacy and safety for the treatment of Covid-19. Overall, the data suggest that Covid-19 patients could benefit from treatments with the antiviral drugs mentioned in this article.

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Author Contributions

Osmar Ignacio Ayala Cáceres, Fernanda Timóteo, Kristiane Fanti Del Pino Santos, Rafael Rodrigo Piva Vasconcelos, and Juliana Jorge contributed with literature survey and manuscript writing. Marco Antonio Utrera Martines and Haroon ur Rashid contributed to the conceptualization, checking, and editing of the manuscript.

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