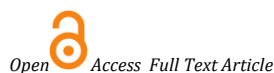
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Review Article

## Therapeutic measures for COVID-19 and their clinical relevance of hERG channel translocation: A Pharmacodynamic approach

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### Abstract



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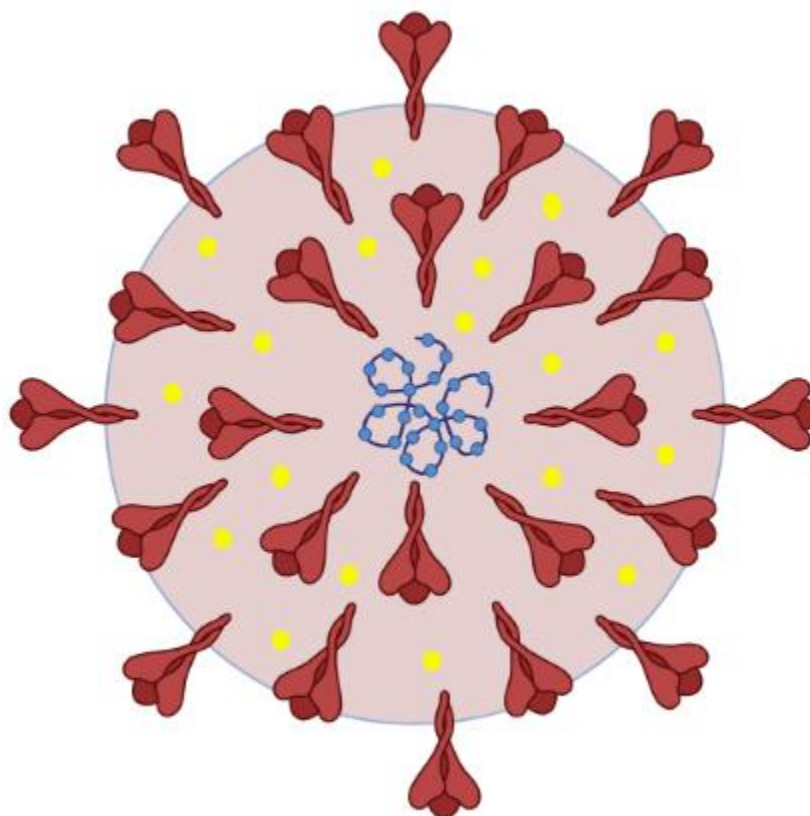
The COVID-19 caused by SARS-CoV-2 poses a massive challenge to the medical system, especially the safe and effective COVID-19 treatment methods, forcing people to look for drugs that may have therapeutic effects as soon as possible. Some old drugs have shown clinical benefits after a few small clinical trials attracting significant attention. Clinically, however, many medications, including those currently shown to be effective against COVID-19, such as Chloroquine, hydroxychloroquine, azithromycin and lopinavir/ritonavir, may cause cardiotoxicity by acting on cardiac potassium channel, hERG channel due to their off-target effect. Blocking of hERG prolongs QT intervals on the electrocardiogram and thus might induce severe ventricular arrhythmias and even sudden cardiac death. Therefore, while focusing on the efficacy of COVID-19 drugs, the fact that they block hERG from causing arrhythmias cannot be ignored. To develop safe and effective drugs, it is necessary to understand the interactions between drugs and hERG channels and the molecular mechanism behind this high affinity. In this review, we focus on the biochemical and molecular mechanistic aspects of related drug blockade in the hERG, trying to provide insights into the QT interval prolongation caused by potential therapeutic drugs for COVID-19 and hope to weigh the risks and benefits when using related drugs.

**Keywords:** COVID-19; Therapeutic measures; hERG channel; Pharmacodynamic; Vaccines

### Introduction

A novel coronavirus disease known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; formerly known as 2019-nCoV) that causes illness<sup>1</sup>. The angiotensin-converting enzyme 2 (ACE2) receptor is the target of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is an RNA virus genetically belonging to the genus Betacoronavirus<sup>2</sup>. The serine protease TGRBSS2 increases viral entrance into the cell after binding. Corona viruses (Omicron, Delta, Alpha, and Beta) are a varied group of viruses that can infect a wide range of animals and cause mild to severe respiratory illnesses in humans. Two highly pathogenic zoonotic coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), caused fatal respiratory illness in humans in 2002 and 2012, respectively, making emerging coronavirus a new public health concern in the twenty-first century. Confirm case of covid is 533,816,957, confirm death due to covid-19 are 6,309,633 and total vaccine administered are 11,854, 673,610 data given by WHO. The newly detected coronavirus, known as "COVID-19," can cause

pneumonia and, like other respiratory viruses, has a 2 to 14-day incubation period<sup>3</sup>. Several health facilities in Wuhan, Hubei Province, China, reported clusters of patients with pneumonia of unknown origin in late December 2019. These patients, like those with SARS and MERS, had symptoms of viral pneumonia, such as fever, cough, and chest pain, as well as dyspnea and bilateral lung infiltration in severe instances. The complete size of the SARS-CoV-2 S protein is 1,273 amino acids, which is longer than SARS-CoV (1,255 amino acids) and known other SARS-CoVs (1,245–1,269 amino acids). It differs from the S proteins of most members of the subgenus Sarbecovirus, with 76.7–77.0 percent amino acid sequence similarity to SARS-CoV from civets and humans, 75–97.7% amino acid sequence similarity to bat coronaviruses in the same subgenus, and 90.7–92.6 percent amino acid sequence similarity to pangolin coronaviruses<sup>4</sup>. The amino acid similarity between SARS-CoV-2 and SARS-CoV is only 73 percent in the S protein's receptor-binding domain (RBD). The insertion of four amino acid residues (PRRA) at the junction of S protein subunits S1 and S2 is another unique genomic trait of SARS-CoV-2<sup>5</sup>.



**Figure 1:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

## History and Discovery

On March 11th, 2020, the World Health Organization (WHO) proclaimed the "Coronavirus Disease 2019" (COVID-19) epidemic<sup>6</sup> which initially started in Asia, had become a pandemic. The first known infections from SARS-CoV-2 were discovered in Wuhan, China. The original source of viral transmission to humans remains unclear, as does whether the virus became pathogenic before or after the spillover event<sup>7</sup>. It's still unclear how this virus spread from animal to human populations. The outbreak obviously began epidemiologically at the Wuhan market, and a number of environmental samples from surrounding the live animal portion of the market were later discovered to be positive for SARS-CoV-2, but it may not have really arisen in the market, based on current findings. An elderly and infirm man who experienced symptoms on December 1, 2019, was the first known case of SARS-CoV-2 infection.

## The Structure of SARS-CoV-2

Coronaviruses are members of the *Coronavirinae* subfamily in the *Coronaviridae* family, which includes four genera: Alpha coronavirus, Gamma coronavirus, and Delta coronavirus. CoVs have a single-stranded positive-sense RNA (+ssRNA) genome that is larger than any other RNA virus. The capsid is generated outside the genome by the nucleocapsid protein (N), and the genome is further packed by an envelope made up of three structural proteins: membrane protein (M), spike protein (S), and envelope protein (E). The genome size of

SARS-CoV-2, which was recently sequenced as a member of the coronavirus family, is around 29.9 kb. Spike (S) comprises sixteen non-structural proteins (nsp16) and four structural proteins (S, E, M, and N) in SARS-CoV-2. The combination of nsp12 and template-primer RNA was greatly boosted when nsp7 and nsp8 were present. Nsp9 is a protein that binds to ssRNA. Nsp10 is required for viral mRNA cap methylation. The RNA-dependent RNA polymerase (RdRp), which is a crucial component of coronavirus replication and transcription, is found in Nsp12. The zinc-binding domain in nsp13 participates in the ATP binding process<sup>8</sup>.

## Coronavirus Structure

The COVID-19 was rapidly identified as being caused by a coronavirus that was eventually dubbed SARS coronavirus 2. (SARS-CoV-2)<sup>9</sup> the coronavirus is a virus that belongs to the coronavirus family. It is the sixth coronavirus to infect humans; four of the other coronaviruses (229E, NL63, OC43, and HKU1) only induce minor cold symptoms. The other three, SARS-CoV, MERS-CoV, and SARS-CoV-2, on the other hand, are capable of causing severe symptoms and even death, with fatality rates of 10%, 37%, and 5%, respectively. Despite the fact that COVID-19 is the subject of numerous investigations and clinical trials around the world<sup>9,10</sup> As the pandemic grows, finding a particular COVID-19 treatment is important, and vaccines targeting several SARS-CoV-2 proteins are now being developed. SARS-CoV-2 is an RNA-enveloped single-stranded virus<sup>11</sup>.

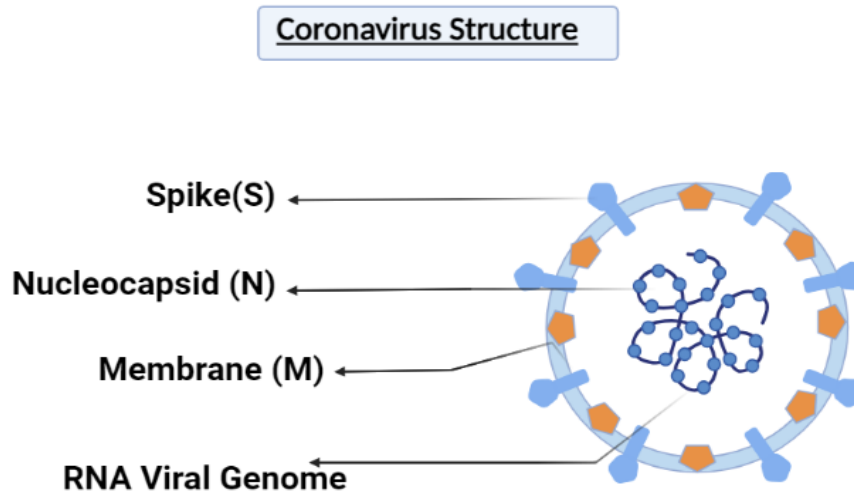


Figure 2: Structure of Coronavirus

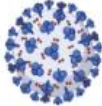

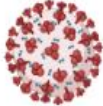

Its whole genome, which is 29,881 bp long (GenBank no. MN908947) and encodes 9860 amino acids, was characterized using an RNA-based metagenomic next-generation sequencing technique<sup>12</sup>. One study looked at the genomes of SARS-CoV-2 and related isolates from the GISATD and NCBI, as well as the coding sequences of spike protein (S), nucleoprotein (N), and polyproteins (P) from additional SARS-CoV-2 isolates, finding 4, 2, and 22 amino acid residue changes in S, N, and P, respectively. At least two SARS-CoV-2 strains are implicated in the outbreak, according to the findings. SARS-CoV shares 79.5 percent sequence identity with the genome sequences. SARS-CoV-2 is not the same as SARS-CoV. Acute respiratory distress syndrome (SARDS) is a severe form of acute respiratory distress the ongoing coronavirus illness 2019 (COVID-19) pandemic is caused by Coronavirus 2 (SARS-CoV-2). Upstream ORFs that are anticipated to play a regulatory role, numerous in-frames internal ORFs within existing ORFs that result in N-terminally truncated products, and internal out-of-frame ORFs that generate unique polypeptides are all examples of these ORFs. We further show that viral mRNAs are not translated more efficiently than host mRNAs rather, due to the enormous

amounts of viral transcripts, virus translation dominates host translation. SARS-CoV-2 and SARS-like coronavirus strain BatCov RaTG13 share 96 percent of their genomic nucleotides. There have been 13 mutations found in the spike protein thus far. Special attention should be paid to the mutation D614G. Spike D614G, a mutation, first appeared in Europe in early February. When it was introduced to new areas, it quickly displaced the original strain, eventually becoming the dominant strain<sup>13</sup> SARS-CoV-2 with the D614G mutation is eight times more effective at transducing cells than wild-type spike protein in numerous cell lines, indicating that the D614G mutation in SARS-CoV-2 spike protein could boost the transduction of multiple human cell types<sup>14</sup>.

**Variants of COVID-19**

Viruses, such as SARS-CoV-2, evolve throughout time and will continue to evolve as they spread. Virus variations can emerge from time to time. A variation is a virus that differs from the original virus in at least one way.

Table 1: Covid-19 variant

	 OMICRON	 DELTA	 ALPHA	 BETA
FIRST DETECTION	NOVEMBER 2021	DECEMBER 2020	SEPTEMBER 2020	MAY 2020
COUNTRY	SOUTH AFRICA	INDIA	UNITED KINGDOM	SOUTH AFRICA
PANGO LINEAGE	8.1.1.529	8.1.6.17.2	8.1.1.7	8.1.35.1
REINFECTION RISK	HIGH	HIGH	HIGH	HIGH

These are variants of covid 19 Alpha (B.1.1.7 and Q lineages), Beta (B.1.351 and descendent lineages), Gamma (P.1 and descendent lineages), Delta (B.1.617.2 and AY lineages), Epsilon (B.1.427 and B.1.429), Eta (B.1.525), Iota (B.1.526), Kappa (B.1.617.1), Mu (B.1.621, B.1.621.1), Zeta (P.2)<sup>15</sup>.

## Mode of Transmission

The most common way for humans to become infected with SARS-CoV-2 (the virus that causes COVID-19) is by contact with infectious respiratory fluids. There are three main methods to be exposed: (1) inhalation of extremely small respiratory droplets and aerosol particles, (2) Direct splashes and sprays depositing respiratory droplets and particles on exposed mucous membranes in the mouth, nose, or eye, (3) contacting mucous membranes with hands that have been soiled by virus-infected respiratory fluids or indirectly by touching virus-infected surfaces. Exhalation releases respiratory fluids in the form of droplets of various sizes (e.g., calm breathing, speaking, and singing, exercising, coughing, and sneezing). Viruses are carried by these droplets, which spread illness. Within seconds to minutes, the larger drops settle out of the air. The tiniest very thin droplets, as well as the aerosol particles created when these fine droplets quickly dry, are so minuscule that they can float in the air for minutes to hours. Infectious exposures to SARS-CoV-2-infected respiratory secretions can arise in three ways (not all of which are mutually exclusive: Inhalation of air containing infectious virus in the form of very small fine droplets and aerosol particles. Within three to six feet of an infectious source, where the concentration of these very small droplets and particles is highest, the risk of transmission is greatest.

### Deposition:

Exhaled viral droplets and particles deposit virus on exposed mucous membranes (i.e., "splashes and sprays," such as being

coughed on). Close to an infectious source, where the concentration of these inhaled droplets and particles is highest, the risk of transmission is also highest.

### Touching:

Contacting mucous membranes with hands soiled by virus-infected exhaled respiratory secretions or from touching virus-infected inanimate surfaces<sup>16</sup>.

## Drug Used During Covid-19

COVID-19 Treatment Guidelines are provided by the National Institutes of Health (NIH) to assist healthcare providers in working with their patients and determining the best treatment options for them. COVID-19 can be treated at home or in an outpatient environment in a variety of ways.

### Antiviral agents:

Many protease inhibitors, such as darunavir and atazanavir, which are already used to treat HIV, might inhibit SARS-CoV-2 from replicating by inactivating the proteases, which are essential for replication. The Italian Medicines Agency (Agenzia Italiana del Farmaco - AIFA) has given the go-ahead for the ARCO-Home study, which aims to evaluate the effectiveness of home treatments such as hydroxychloroquine, lopinavir-ritonavir, favipiravir, and darunavir-cobicistat in treating early COVID-19 patients without the need for hospitalisation or invasive procedures like intubation<sup>17</sup>.

**Table 2:** Various drugs and their routes of administration for the treatment of covid-19

Treatment	Who	When	How
Nirmatrelvir with Ritonavi (Paxlovid) Antiviral	Adults; children 12 years and older	Start as soon as possible; must begin within 5 days of when symptoms start	Taken at home by mouth (orally)
Remdesivir (Veklury) Antiviral	Adults and children	Start as soon as possible; must begin within 7 days of when symptoms start	Intravenous (IV) infusions at a healthcare facility for 3 consecutive days
Bebtelovimab Monoclonal antibody	Adults, children 12 years and older	Start as soon as possible; must begin within 7 days of when symptoms start	Single IV injection
Molnupiravir (Lagevrio) Antiviral	Adults age 18 years and older	Start as soon as possible; must begin within 5 days of when symptoms start	Taken at home by mouth (orally)
Invermectin	Adult age	Start as soon as possible; must begin within 5 days of when symptoms start	Taken at home by mouth (orally)
Vitamin-c (500mg)	Adult age	Start as soon as possible; must begin within 5 days of when symptoms start	1 to 2 in a day( orally) for 5days
Zink (220mg)	Adult age	Start as soon as possible; must begin within 5 days of when symptoms start	Twice a day (orally)for 5days
Pentop (20mg)	Adult age	Start as soon as possible; must begin within 5 days of when symptoms start	Taken at home by mouth (orally) for 5 days
Cetirizine	Adult age	Start as soon as possible; must begin within 5 days of when symptoms start	Taken at home by mouth (orally) for 5 days
PCM	Adult age	Start as soon as possible; must begin within 5 days of when symptoms start	Take twice a day at home by mouth (orally) for 5days

### Chloroquine/hydrochloroquine:

Both chloroquine and hydroxychloroquine (HCQ) are weak bases that are mostly found in a protonated state with a positive charge in the extracellular environment. They are

unable to pass the plasma membrane due to their positive charge. In the acidic, low-pH organelles like endosomes, Golgi vesicles, and lysosomes, the non-protonated fraction that enters a cell is immediately protonated. Additionally, chloroquine phosphate showed promise in the control of the

SARS-CoV and Zika virus outbreaks<sup>18</sup>. Through the action of acidic hydrolases in the lysosomes, macromolecule production in the endosomes, and post-translational protein modification in the Golgi apparatus, chloroquine alters the pathways by which proteins degrade. Chloroquine inhibits antigen processing in macrophages and other antigen-presenting cells, which leads in an antirheumatic response<sup>19</sup>.

#### Azithromycin:

The reason behind the use of AZM against inflammatory symptoms that cause interstitial lung disease is its immunomodulation capabilities. By preventing the production of many cytokines linked to COVID-19 severe respiratory syndrome, AZM has an intriguing immunomodulatory profile. It is true that AZM controls and/or lowers the levels of IL-1, IL-6, IL-8, IL-10, IL-12, and IFN- $\alpha$ <sup>20</sup>.

#### Remdesivir:

Remdesivir is a once-daily nucleoside ribonucleic acid polymerase inhibitor that prevents the reproduction of the coronavirus 2 that causes severe acute respiratory syndrome. Remdesivir has received permission for treatment in adults and children hospitalized with severe coronavirus illness in a number of nations in 2019. Remdesivir is subjected to metabolic activation inside the cell, resulting in the formation of the intracellular active triphosphate metabolite GS-443902 (detected in peripheral blood mononuclear cells), and finally the renally removed plasma metabolite GS-441524. The pre-clinical pharmacology of RDV, clinical pharmacokinetics, pharmacodynamics/concentration-QT analysis, rationale for dose selection for treating patients with COVID-19, and potential drug-drug interactions based on available in vitro and clinical data in healthy volunteers are all covered in this review. Following a 3-225 mg single-dose intravenous infusion of an RDV solution formulation over a two-hour period. The results supported this clinical dosage schedule for the treatment of COVID-19 because they revealed significant intracellular concentrations of GS-443902, which is suggestive of an effective conversion from the RDV into the triphosphate form. RDV has a limited potential for drug-drug interactions, according to mathematical projections based on in vitro and phase I data, as the effect of inducers or inhibitors on RDV distribution is reduced by the parenteral mode of administration and thorough extraction. RDV is not projected to be a clinically relevant inhibitor of drug-metabolizing

enzymes or transporters in individuals infected with COVID-19 at therapeutic RDV levels, according to physiologically based pharmacokinetic modeling.

#### Nirmatrelvir/Ritonavir:

Nirmatrelvir/ritonavir received an EUA for the treatment of mild-to-moderate COVID-19 in adults and pediatric outpatients (aged 12 years and older and weighing at least 40 kg) who are at high risk of severe COVID-19, which could result in hospitalizations or death.

#### Molnupiravir:

Is the oral form of beta-D-N4-hydroxycytidine (NHC), an RNA virus-specific ribonucleoside with wide antiviral action. Viral mutations and fatal mutagenesis are caused by NHC absorption by viral RNA-dependent RNA-polymerases.

#### Tocilizumab:

A humanized monoclonal antibody called tocilizumab has been studied for its effectiveness in treating severe COVID-19 because it can target the IL-6 receptor in both its membrane-bound and soluble versions<sup>21</sup>. Use of tocilizumab resulted in a quick and lasting response as well as a considerable clinical improvement. Patients using tocilizumab had greater levels of two cytokine storm biomarkers, C-reactive protein (CRP) and IL-6<sup>22</sup>.

#### Baricitinib:

Another cytokine-release inhibitor, baricitinib, appears to be a promising anti-inflammatory medication. It is a Janus kinase inhibitor (anti-JAK) with a solid safety and effectiveness track record that is approved for the treatment of rheumatoid arthritis (RA). Additionally, it appears to have antiviral effects due to its affinity for the SARS-CoV-2 endocytosis-reducing AP2-associated protein AAK1<sup>23</sup>.

### Mechanism of Action

#### Nirmatrelvir/ritonavir:

Nirmatrelvir is an orally accessible protease inhibitor that inhibits MPRO, a viral protease that cleaves the two viral polyproteins required for viral replication<sup>24</sup>.

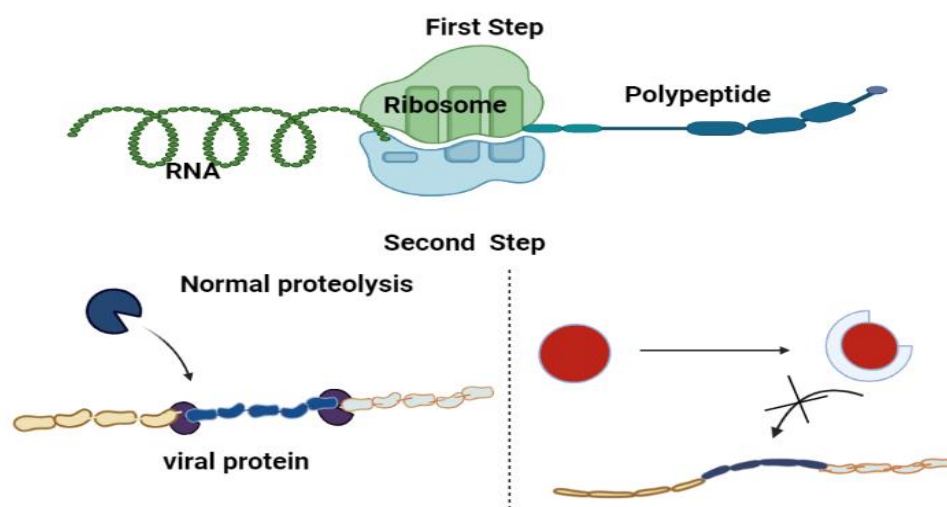
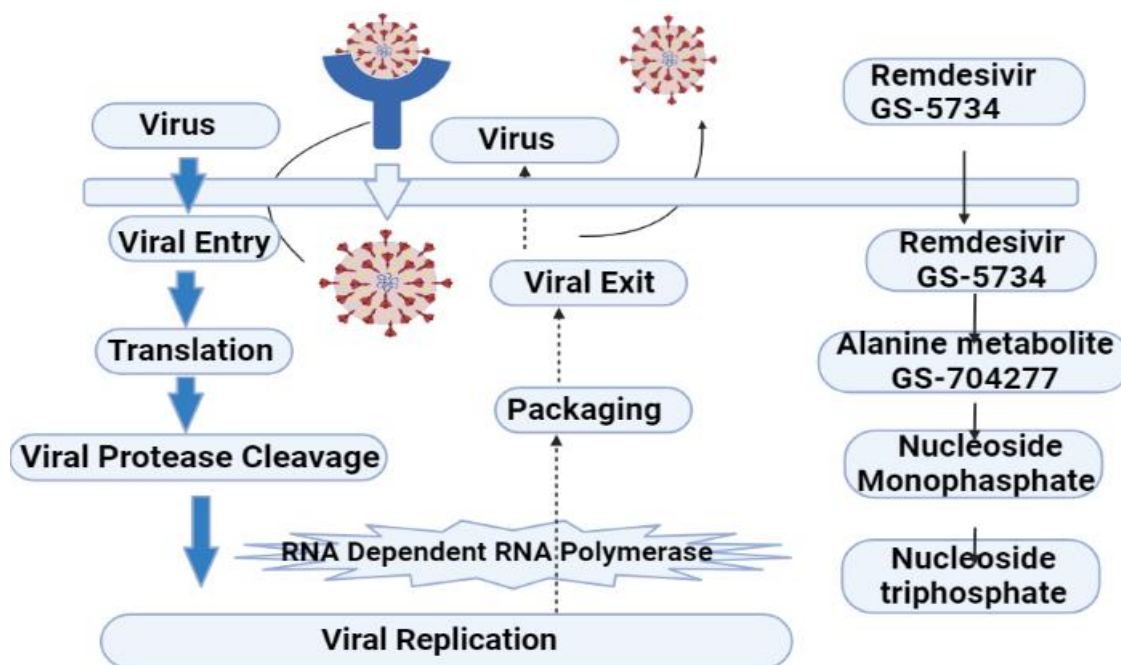


Figure 3: Mechanism of action of ritonavir

**Molnupiravir:**

Molnupiravir inhibits the reproduction of a variety of viruses, including SARS-CoV, including SARS-CoV-2. SARS-CoV-2 replication is inhibited in human lung tissue, SARS-CoV-2 transmission is blocked in ferrets and SARS-CoV-2 RNA is reduced in patients<sup>25</sup>.



**Figure 4:** Mechanism of action of remdesivir

**Remdesivir:**

They discovered that remdesivir inhibits a specific enzyme necessary for viral replication. Coronaviruses replicate by employing an enzyme called RNA-dependent RNA polymerase to copy their genetic material<sup>26</sup>.

**Tocilizumab:**

Tocilizumab, a monoclonal antibody that can block the IL-6 receptor, has a bright future. Based on the results of various CRS studies<sup>27,28</sup>, Tocilizumab mechanism of action in the treatment of COVID-19 is unknown. IL-6 is secreted by almost all stromal cells and immune system cells, including B lymphocytes, T lymphocytes, macrophages, monocytes, dendritic cells, mast cells, and other non-lymphocytes like fibroblasts, endothelial cells, keratinocytes, glomerular meningeal cells, and tumor cells, according to previous studies<sup>29</sup>. The body's level of IL-6 is quite low under normal circumstances, but it can be swiftly produced to increase the body's defense function when an infection or injury occurs. CRS is caused by excessive IL-6 secretion, and the more severe the CRS, the greater the IL-6 serum peak concentration. To initiate signal transduction and stimulate downstream signal transduction and gene expression, IL-6 forms a complex with its receptor IL-6R and then attaches to the signal transducer glycoprotein 130 (gp-130). There are two types of IL-6R: membrane-bound (mIL-6R) and soluble (IL-6R) (sIL-6R). In the traditional signal transduction route, IL-6 forms a complex with mIL-6R and then binds to gp-130, resulting in downstream Reactions Anti-inflammatory actions, for example, are restricted to cells that express mIL-6R. IL-6 forms a complex with sIL-6R and gp-130 in the trans-signaling pathway, which activates intracellular signal transduction in the absence of mIL-6R and has inflammatory effects<sup>30</sup>. The next step was to stimulate the production of acute reactive protein via two distinct signaling mechanisms. The JAK/STAT tyrosine kinase system mediates one IL-6 signaling pathway, whereas the Ras/mitogen-activated protein kinase (MAPK)/NF-B-IL-6 pathway mediates the other. The former is a significant route<sup>31,32</sup>. Many cells cannot respond to IL-6

signal due to the lack of expression of IL-6R in the traditional signal pathway, but some of these cells can be stimulated by the sIL-6R-IL-6 complex to respond to IL-6 signal and cause cell signal transduction<sup>33</sup>. Extracellular gp-130 suppresses the trans-presentation signal, and extracellular gp-130 can form a complex with sIL-6R to prevent sIL-6R from interacting with membrane-bound gp-130. The classical signal is restricted to cells that express IL-6R (macrophages, neutrophils, T cells, etc.) and plays a key role in the low level of IL-6. However, because gp-130 is present everywhere, when the amount of IL-6 rises, the IL-6 signal is extensively expressed. IL-6 Trans signaling via the sIL-6R can then activate practically all cells in the body and regulate pro-inflammatory responses in this way. In a range of preclinical chronic and autoimmune illness models, blocking trans-signaling proved successful. Tocilizumab, a humanized anti-IL-6R monoclonal antibody, binds to both mIL-6R and sIL-6R, inhibiting both classical and trans-signals. This could be a possible strategy for treating cytokine storm in COVID-19<sup>34</sup>.

**Vaccines**

It is urgent to develop effective and safe vaccines to control the new occurrence of COVID-19 and to reduce SARS-CoV-2-infection-related morbidity and mortality<sup>35</sup>. Almost one billion people in low-income nations are still unvaccinated as of May 22, 2022. Only 57 countries practically all of them high-income countries have immunized 70% of their population (WHO).

**Corbevax:**

In phase 1 and 2 investigations, Biological E's CORBEVAX™ vaccine, which comprises the protein subunit of the receptor binding domain (RBD) from the spike protein of SARS-COV-2,

was chosen and shown to be safe, well tolerated, and immunogenic in healthy adult populations.

#### **Covaxin:**

Bharat Biotech produced COVAXIN, India's indigenous COVID-19 vaccine, in conjunction with the Indian Council of Medical Research (ICMR) - National Institute of Virology (NIV). The vaccine is being developed using a platform derived from Whole-Virion Inactivated Vero Cells. Because inactivated vaccinations do not multiply, they are unlikely to revert and cause disease. They include dead viruses that are unable to infect humans but can nevertheless teach the immune system to mount a defensive response in the face of infection. It's a two-dose immunization schedule that's spread out over 28 days. It's a vaccination that doesn't require sub-zero storage, doesn't require reconstitution, and comes in ready-to-use liquid form in multi-dose vials that's stable at 2-8 degrees Celsius. In July 2020, the vaccine gained DCGI approval for Phase I and II Human Clinical Trials<sup>36</sup>.

#### **Covishield:**

It's a chimp adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein that's recombinant and replication-deficient. It is divided into two 0.5 ml doses. COVISHIELD TM must be taken in both doses for maximum protection. The following are contraindications to receiving a second dose of vaccine: After a previous injection of this vaccination, I had a severe adverse response. If your doctor diagnosed your reaction as a severe allergic reaction to the vaccine, you should not receive a second dose. You can take the second dose if you have any more side events (known or unknown) after the first dose. Following the first dose of vaccination, patients who had severe blood clotting (venous and/or arterial thrombosis) and a low platelet count (thrombocytopenia). In clinical trials, COVISHIELD TM was given to persons with and without comorbid illnesses, and the safety profile was similar in both groups (e.g.: Hypertension, Cardiovascular Disease, Asthma, Diabetes, etc.). The vaccine is only available to people who have clinically stable comorbid illnesses. Before receiving the vaccination, please see your treating physician for a risk-benefit analysis based on clinical judgment. The vaccine is not contraindicated if you have a history of G6PD deficiency. Before getting the vaccine, make sure to check with your doctor for a risk-benefit analysis based on clinical judgment<sup>37</sup>.

#### **The Janssen COVID-19**

Vaccine (Janssen Biotech, Inc., a Janssen Pharmaceutical company, Johnson & Johnson; New Brunswick, New Jersey) received an emergency use authorization (EUA) from the Food and Drug Administration (FDA) on February 27, 2021, and the Advisory Committee on Immunization Practices (ACIP) issued interim recommendations for its use in people over the age of 18 on February 28. Following reports of six occurrences in the United States of cerebral venous sinus thrombosis (CVST) with thrombocytopenia, a rare thromboembolic condition, in people who had received the Janssen COVID-19 vaccination, the CDC and FDA advised against using the vaccine on April 13, 2021. Two urgent ACIP meetings were quickly called to assess instances of thrombosis with thrombocytopenia syndrome (TTS) that had been reported and to discuss revised guidelines for the use of the Janssen COVID-19 vaccination in the US. On April 23, 2021, ACIP reiterated its intermediate recommendation for the use of Janssen COVID-19 vaccine in all individuals aged 18 years under the FDA's EUA. This recommendation now includes a warning that uncommon clotting events may occur following immunization, mostly among women aged 18–49 years. The risk for TTS associated with the Janssen COVID-19 vaccine, particularly in women over 50, as well as the availability of alternative COVID-19

vaccines must be discussed with patients and healthcare providers in order to help them make informed vaccine decisions and ensure early diagnosis and clinical management of TTS<sup>38</sup>.

#### **Moderna:**

The severe acute respiratory syndrome coronavirus 2's perfusion stabilized full-length spike protein is encoded by the mRNA-based vaccination known as mRNA-1273 (Moderna) (SARS-CoV-2)<sup>39</sup>. By encapsulating the mRNA into lipid nanoparticles (LNPs), which shield the mRNA from RNases' destruction, the efficacy of these vaccines has been maximised<sup>40</sup>.

#### **Primary Series:**

In the primary series, 2 doses of Moderna are given 4–8 weeks apart. People who are immunocompromised (have a weakened immune system) should receive a third dose at least four weeks following the second dosage in the initial series.

**Boosters:** A booster should be given to everybody who obtained a Moderna primary series. A second booster dose is only available to a select few people. To find out if and when you can obtain boosters for your COVID-19 immunizations, use the CDC's COVID-19 booster tool.

#### **Novavax:**

According to preliminary results from clinical studies, the SARS-CoV-2 vaccine made by the US biotechnology company Novavax is 95.6% effective against the original strain of SARS-CoV-2 and also offers protection against the later variants B.1.1.7 (85.6%) and B.1.351 (60%) of the virus. According to preliminary results from clinical studies, the SARS-CoV-2 vaccine made by the US biotechnology company Novavax is 95.6% effective against the original strain of SARS-CoV-2 and also offers protection against the later variants B.1.1.7 (85.6%) and B.1.351 (60%) of the virus<sup>41</sup>. Nuvaxovid (NVX-CoV2373) and Covovax (NVX-CoV2373) vaccines against COVID-19 were listed for emergency use by the Technical Advisory Group for Emergency Use Listing on December 20, 2021 and December 17, 2021, respectively. The Novavax vaccine will be produced in two separate locations. The vaccine will be manufactured under the trade name Nuvaxovid in Europe and has been approved by the European Medicines Agency, while it will be manufactured under the trade name Covovax in India by Serum Institute of India and has been approved by the Drugs Controller General of India. The WHO's Strategic Advisory Group of Experts on Immunization (SAGE) has produced interim vaccine policy recommendations for the Novavax (NVX-CoV2373) vaccine. The interim recommendations are summarized in this article. There is currently no information on the safety and efficacy of the Novavax (NVX-CoV2373) vaccination in pregnant women. However, efficacy is likely to be equivalent to non-pregnant women of a similar age based on recent findings from other protein-based vaccines during pregnancy.

#### **Sputnik Light:**

Recent developments include the registration and approval for use in Russia of the single-component Sputnik Light vaccine, which is the first part of the Sputnik V vaccine (recombinant human adenovirus serotype 26 containing the gene of the SARS-CoV-2 spike (S) protein(ClinicalTrials.gov identifier NCT04741061)<sup>42</sup>. In an open, non-randomized, 1/2 Phase study, Sputnik Light was very well tolerated and elicited potent humoral and cellular immune responses in both seronegative and seropositive subjects<sup>43</sup>.

### Sputnik-V:

The Russian Gamaleya National Center of Epidemiology and Microbiology created the Sputnik V COVID-19 vaccine, also known as Gam-COVID-Vac. It is a two-part vaccination using an adenovirus (Ad) viral vector to promote the development of antibodies against the spike protein (S)<sup>44</sup>. Ads serve as the delivery vehicle for the DNA instructions to produce the S of the SARS-CoV-2 virus in the body. They have been designed to enter cells but not multiply. Sputnik V is composed of two distinct Ads, Ad26 and Ad5, both of which are administered independently, three weeks apart, and both of which are carriers of the SARS-CoV-2 glycoprotein S gene. To increase the effectiveness of the vaccination, Ad26 is used in the first dosage and Ad5 in the second. By using two separate vectors, the risk of the body producing Ad antibodies after the first dosage is reduced; this might render the second dose ineffective<sup>45</sup>. According to the manufacturer's statement, the Sputnik V vaccine is exclusively manufactured using non-replicating Ad vectors of type E1 and E3, which are created and grown on HEK293 cells<sup>46</sup>.

### ZyCoV-D:

India's Ahmedabad-based Cadila Healthcare Limited produced the ZyCoV-D vaccine. The DNA vaccine candidate for SARS-CoV-2 is a DNA plasmid vector called pVAX1 that carries a gene that expresses the spike-S protein of the virus as well as an IgE signal peptide. The submitted Wuhan Hu-1 isolate's spike gene region was chosen (Gene bank Accession No. MN908947.3). The SARS-CoV-2 DNA vaccine construct was produced using the pVAX-1 plasmid vector. Spike regions and the signal peptide gene were chemically created and introduced into the pVAX-1 plasmid DNA vaccination vector. After receiving the plasmid DNA constructions, the construct was transformed in DH5-alpha<sup>TM</sup> chemically competent cells. The National Regulatory Authority-approved manufacturing facility used current Good Manufacturing Practices to replicate the DH5-alpha E coli containing the plasmid DNA for large-scale production. Five mg of DNA plasmid containing spike protein gene region insert from SARS-CoV-2 virus are suspended in phosphate buffer saline in each 0.5 mL of ZyCoV-D vaccine<sup>47</sup>.

### Drug Act via hERG Channel:

The potassium channel Kv11.1 or the ERG1 are other names for the hERG channel. The three-phase repolarization of the ventricular action potential, or cardiac myocyte repolarization, is mediated by the pore-forming alpha subunit of a fast component of the delayed rectifier potassium channel (IKr), which is encoded by the hERG gene<sup>48</sup>. hERG channel failure causes a partial or total reduction in the IKr current, resulting in a prolonged action potential duration (APD) on an ECG and if the extension exceeds the normal range (440 ms in men, 460 ms in women), LQTS occurs<sup>49</sup>. LQTS caused by hERG deficiency is referred to as type 2 LQTS (LQT2) in clinical terms, and it is the second most frequent form of LQTS<sup>50</sup>. Increased inward current and weaker outward currents caused by medicines (A) and displayed on an electrocardiogram (ECG) result in a prolonged action potential duration (APD) (B). The hERG channel goes through a brief activation process that includes channel opening, fast inactivation, and recovery from inactivation. The channel reopens at this point, followed by a gradual deactivation process to seal it. The channel must be open for drug binding to occur, and when it is closed, the drug is trapped by the blocking action and released when the channel reopens (C). The electrical activity of the heart is mediated by the regulation of the channels in which ions flow

into and out of cardiomyocytes. Theoretically, ion currents that constitute the ventricular action potential include inward and outward currents, and the balance of outward and inward currents is the key to the formation of normal APD. Na<sup>+</sup> and L-type Ca<sup>2+</sup> currents (I<sub>Na</sub> and I<sub>CaL</sub>, respectively) are the most important inward currents in cardiomyocytes, and the K<sup>+</sup> current (I<sub>K</sub>) is the major outward current. Increased inward current or a weakening of outward currents due to drug effects can result in a prolongation of APD, leading to a prolonged QT interval<sup>51</sup>. Excessive prolongation can facilitate the production of early after depolarization (EAD) in three-phase repolarization that will trigger TdP and even ventricular fibrillation if EAD reaches its threshold<sup>52</sup>.

### Mechanism Linking Cardiac Arrest with Covid-19

cardiac causes of CA in covid-19 infection. Figure depicts the conditions linked to Covid-19-related CA. Because the focus of this review is on the pathophysiology of Covid-19-related cardiac arrest, a detailed discussion of the cardiovascular consequences of Covid-19 infection in general is beyond the scope of this paper. Covid-19 has the potential to disrupt the cardiovascular system both directly and indirectly, resulting in problems such as acute myocardial infarction, acute cardiac injury, myocarditis, arrhythmias, and acute heart failure<sup>53</sup>. In agreement with prior evidence from different SARS viruses, the presence of Covid-19 viral components in endothelial cells with endotheilitis-like features has been reported<sup>54</sup>.

### Drug cardiac toxicity related to cardiac arrest in Covid-19 infection:

Depicts the medications that are currently being used or studied to treat Covid-19 infection, which could lead to CA either directly or indirectly. Arrhythmias are the most common symptom in individuals with Covid-19 infection who are predisposed to CA and are the most common cardiac medication toxicity associated with Covid-19 treatment<sup>55</sup>. Arrhythmias are caused by cardiac injury, heart failure, metabolic derangements, and neurohormonal or inflammatory stress caused by the viral infection and hypoxemia, and is attributed to cardiac injury, heart failure, metabolic derangements, and neurohormonal or inflammatory stress caused by the viral infection and hypoxemia<sup>54</sup>. Patients with elevated troponin T levels with Covid-19 infection were shown to have a higher rate of malignant arrhythmias (ventricular tachycardia or ventricular fibrillation). In terms of electrolytic imbalances, people with Covid-19 infection have been found to have hypokalemia, which is commonly accompanied by gastrointestinal complaints<sup>56</sup>. QT prolongation is common in Covid-19 infection, regardless of electrolytes, and has been associated to systemic inflammation. Through cytokine-mediated cardiac electrical remodeling, regardless of concomitant antimicrobial therapy, the latter causes considerable QTc prolongation, which is quickly reversed after lowering C-reactive protein and cytokine levels). Furthermore, higher interleukin-6 (IL-6) levels contribute to the risk of QTc prolongation by suppressing IKr in heterologous cells and myocyte, which increases the risk of QTc prolongation. In response to myocardial ischemia, IL-6 levels rise. It is a symptom of the disease's severity and poor prognosis. In support, Patients with cardiovascular signs of Covid-19 infection, such as myocardial ischemia and myocarditis, have been found to have QT prolongation. Toxicity of drugs in Covid-19 patients linked to cardiac arrest.



**Table 3:** Mechanism of actions and risk factors of cardiac arrest drugs

Pharmaceutical agent	Mechanism related to cardiac arrest	Ongoing Clinical Trials	Interactions with drugs enhancing risk of cardiac arrest*
Chloroquine/ Hydroxychloroquine*	Causes QT prolongation by blocking the hERG potassium channel (common mechanism) and TdP	Phase 2/3/4	CYP3A4 substrate
	Associated with HF, conduction system abnormalities, cardiomyopathy, hypokalemia, diarrhea		Severe with amiodarone, flecainide, mexiletine, sotalol, dofetilide
Pharmaceutical agent	Causes QT prolongation by blocking the hERG potassium channel and TdP	Phase 2/3/4	Weak CYP3A4 inhibitor, Severe with amiodarone, flecainide, disopyramide, sotalol, dofetilide, propafenone
Chloroquine/ Hydroxychloroquine*	Causes cardiac conduction abnormalities	Phase 2/3/4	CYP3A4 inhibitor and substrate
	May cause QT prolongation May cause electrolytic imbalances due to vomiting and diarrhea		Severe with amiodarone, dronedarone, disopyramide,

## Conclusions:

COVID-19 is considered a potentially preventable disease. Many countries have implemented multiple infection control measures. Many governments face uncertainties about how to prioritize at this time when the pandemic appears to be in transition but when the risk of new variants and future surges remains real. So many drugs have been repurposed and already employed for effective COVID-19 treatment. Still, no specific and effective cure has been confirmed and approved by the regulatory authorities to treat this disease. Many monoclonal antibodies those act via various mechanisms on inflammatory cytokines. These include Tocilizumab, Sarilumab (IL-6 receptor antagonist) and  $\alpha$ , and  $\beta$ - interferon therapy was proved successful, especially when combined with other anti-viral oral drugs. The current research revealed that “one hundred seventy-two” countries are doing their research for the development of an effective and safe vaccine against SARS-CoV-2. In the recent future, it is expected that the efforts of researchers and scientists will see the light of day.

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## References

- Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. *Lancet Infect Dis.* 2020;20(4):398-400. [https://doi.org/10.1016/S1473-3099\(20\)30141-9](https://doi.org/10.1016/S1473-3099(20)30141-9) PMID:32113510
- Matricardi PM, Dal Negro RW, Nisini R. The first, holistic immunological model of COVID-19: implications for prevention, diagnosis, and public health measures. *Pediatr Allergy Immunol.* 2020;31(5):454-470. <https://doi.org/10.1111/pai.13271> PMID:32359201 PMID:PMC7267459
- Virlogeux V, Fang VJ, Park M, Wu JT, Cowling BJ. Comparison of incubation period distribution of human infections with MERS-CoV in South Korea and Saudi Arabia. *Sci Rep.* 2016;6(1):1-7. <https://doi.org/10.1038/srep35839> PMID:27775012 PMID:PMC5075793
- Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature.* 2020;579(7798):270-273. <https://doi.org/10.1038/s41586-020-2012-7> PMID:32015507 PMID:PMC7095418
- Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. *Nat Med.* 2020;26(4):450-452. <https://doi.org/10.1038/s41591-020-0820-9> PMID:32284615 PMID:PMC7095063
- Fan J, Liu X, Pan W, Douglas MW, Bao S. Epidemiology of coronavirus disease in Gansu Province, China, 2020. *Emerg Infect Dis.* 2020;26(6):1257. <https://doi.org/10.3201/eid2606.200251> PMID:32168465 PMID:PMC7258465
- Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* 2020; 382:727-733. <https://doi.org/10.1056/NEJMoa2001017> PMID:31978945 PMID:PMC7092803
- Wang MY, Zhao R, Gao LJ, Gao XF, Wang DP, Cao JM. SARS-CoV-2: structure, biology, and structure-based therapeutics development. *Front Cell Infect Microbiol.* 2020;10:01-17 <https://doi.org/10.3389/fcimb.2020.587269> PMID:33324574 PMID:PMC7723891
- Wu C, Liu Y, Yang Y, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharm Sin B.* 2020;10(5):766-788. <https://doi.org/10.1016/j.apsb.2020.02.008> PMID:32292689 PMID:PMC7102550
- Liu C, Zhou Q, Li Y, et al. Research and development on therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases. *ACS Cent Sci.* 2020 Mar 25; 6(3): 315-331. <https://doi.org/10.1021/acscentsci.0c00272> PMID:32226821 PMID:PMC10467574
- Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet.* 2020;395(10224):565-574. [https://doi.org/10.1016/S0140-6736\(20\)30251-8](https://doi.org/10.1016/S0140-6736(20)30251-8) PMID:32007145
- Chen L, Liu W, Zhang Q, et al. RNA based mNGS approach identifies a novel human coronavirus from two individual pneumonia cases in 2019 Wuhan outbreak. *Emerg Microbes Infect.* 2020;9(1):313-319. <https://doi.org/10.1080/22221751.2020.1725399> PMID:32020836 PMID:PMC7033720
- Korber B, Fischer WM, Gnanakaran S. et al. Tracking changes in SARS-CoV-2 Spike: evidence that D614G increases infectivity of the COVID-19 virus. *Cell* ; 182(4): 812-827. <https://doi.org/10.1016/j.cell.2020.06.043> PMID:32697968 PMID:PMC7332439

14. Cotto KC, Wagner AH, Feng YY, et al. DGIdb 3.0: a redesign and expansion of the drug-gene interaction database. *Nucleic Acids Res.* 2018;46(D1):D1068-D1073. <https://doi.org/10.1093/nar/gkx1143> PMID:29156001 PMCID:PMC5888642
15. Vasireddy D, Vanaparthy R, Mohan G, Malayala SV, Atluri P. Review of COVID-19 variants and COVID-19 vaccine efficacy: what the clinician should know? *J Clin Med Res.* 2021;13(6):317. <https://doi.org/10.14740/jocmr4518> PMID:34267839 PMCID:PMC8256910
16. Liu Y, Ning Z, Chen Y, et al. Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals. *Nature.* 2020;582(7813):557-560. <https://doi.org/10.1038/s41586-020-2271-3> PMID:32340022
17. Stasi C, Fallani S, Voller F, Silvestri C. Treatment for COVID-19: An overview. *Eur J Pharmacol.* 2020;889:173644. <https://doi.org/10.1016/j.ejphar.2020.173644> PMID:33053381 PMCID:PMC7548059
18. Humeniuk R, Mathias A, Kirby BJ, et al. Pharmacokinetic, pharmacodynamic, and drug-interaction profile of remdesivir, a SARS-CoV-2 replication inhibitor. *Clin Pharmacokinet.* 2021;60(5):569-583. <https://doi.org/10.1007/s40262-021-00984-5> PMID:33782830 PMCID:PMC8007387
19. Zhou S, Hill CS, Sarkar S, et al.  $\beta$ -d-N 4-hydroxycytidine inhibits SARS-CoV-2 through lethal mutagenesis but is also mutagenic to mammalian cells. *J Infect Dis.* 2021;224(3):415-419. <https://doi.org/10.1093/infdis/jiab247> PMID:33961695 PMCID:PMC8136050
20. Kabinger F, Stiller C, Schmitzová J, et al. Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. *Nat Struct Mol Biol.* 2021;28(9):740-746. <https://doi.org/10.1038/s41594-021-00651-0> PMID:34381216 PMCID:PMC8437801
21. Magro G. SARS-CoV-2 and COVID-19: Is interleukin-6 (IL-6) the 'culprit lesion' of ARDS onset? What is there besides Tocilizumab? *SGP130Fc. Cytokine X.* 2020;2(2):100029. <https://doi.org/10.1016/j.cyttox.2020.100029> PMID:32421092 PMCID:PMC7224649
22. Tian J, Zhang M, Jin M, et al. Repurposed tocilizumab in patients with severe COVID-19. *J Immunol.* 2021;206(3):599-606. <https://doi.org/10.4049/jimmunol.2000981> PMID:33298617 PMCID:PMC7812057
23. Cantini F, Niccoli L, Matarrese D, Nicastrì E, Stobbione P, Goletti D. Terapia con baricitinib en COVID-19: un estudio piloto sobre seguridad e impacto clínico. *J Infect.* 2020;81:318-356. <https://doi.org/10.1016/j.jinf.2020.04.017> PMID:32333918 PMCID:PMC7177073
24. Duveau DY, Thomas CJ. The Remarkable Selectivity of Nirmatrelvir. *ACS Pharmacol Transl Sci.* 2022; 5(6): 445-447. <https://doi.org/10.1021/acspstci.2c00065> PMID:35702394 PMCID:PMC9128007
25. Kabinger F. Mecanismo de mutagênese de SARS-CoV-2 induzida por molnupiravir. *Struct Mol Biol.* 2021;28(9):740-746. <https://doi.org/10.1038/s41594-021-00651-0> PMID:34381216 PMCID:PMC8437801
26. Nishimura K, Sano M, Ohtaka M, et al. Development of defective and persistent Sendai virus vector: a unique gene delivery/expression system ideal for cell reprogramming. *J Biol Chem.* 2011;286(6):4760-4771. <https://doi.org/10.1074/jbc.M110.183780> PMID:21138846 PMCID:PMC3039346
27. Fitzgerald JC, Weiss SL, Maude SL, et al. Cytokine release syndrome after chimeric antigen receptor T cell therapy for acute lymphoblastic leukemia. *Crit Care Med.* 2017;45(2):124. <https://doi.org/10.1097/CCM.0000000000002053> PMID:27632680 PMCID:PMC5452983
28. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med.* 2018;378(5):439-448. <https://doi.org/10.1056/NEJMoa1709866> PMID:29385370 PMCID:PMC5996391
29. Jones SA, Jenkins BJ. Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer. *Nat Rev Immunol.* 2018;18(12):773-789. <https://doi.org/10.1038/s41577-018-0066-7> PMID:30254251
30. Braun GS, Nagayama Y, Maruta Y, et al. IL-6 trans-signaling drives murine crescentic GN. *J Am Soc Nephrol.* 2016;27(1):132-142. <https://doi.org/10.1681/ASN.2014111147> PMID:26041841 PMCID:PMC4696576
31. Villarino A V, Kanno Y, O'Shea JJ. Mechanisms and consequences of Jak-STAT signaling in the immune system. *Nat Immunol.* 2017;18(4):374-384. <https://doi.org/10.1038/ni.3691> PMID:28323260
32. Zegeye MM, Lindkvist M, Fälker K, et al. Activation of the JAK/STAT3 and PI3K/AKT pathways are crucial for IL-6 trans-signaling-mediated pro-inflammatory response in human vascular endothelial cells. *Cell Commun Signal.* 2018;16(1):1-10. <https://doi.org/10.1186/s12964-018-0268-4> PMID:30185178 PMCID:PMC6125866
33. Johnson DE, O'Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. *Nat Rev Clin Oncol.* 2018;15(4):234-248. <https://doi.org/10.1038/nrclinonc.2018.8> PMID:29405201 PMCID:PMC5858971
34. Rose-John S. The soluble interleukin 6 receptor: advanced therapeutic options in inflammation. *Clin Pharmacol Ther.* 2017;102(4):591-598. <https://doi.org/10.1002/cpt.782> PMID:28675418
35. Mavraganis G, Aivalioti E, Chatzidou S, et al. Cardiac arrest and drug-related cardiac toxicity in the Covid-19 era. *Epidemiology, pathophysiology and management. Food Chem Toxicol.* 2020;145:111742. <https://doi.org/10.1016/j.fct.2020.111742> PMID:32916218 PMCID:PMC7833119
36. Yadav P, Mohandas S, Shete A, et al. Protective efficacy of COVAXIN® against Delta and Omicron variants in hamster model. *bioRxiv.* Published online 2022. <https://doi.org/10.1101/2022.06.14.496021>
37. Voysey M, Clemens SAC, Madhi SA, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet.* 2021;397(10277):881-891. [https://doi.org/10.1016/S0140-6736\(21\)00432-3](https://doi.org/10.1016/S0140-6736(21)00432-3) PMID:33617777
38. MacNeil JR, Su JR, Broder KR, et al. Updated recommendations from the Advisory Committee on Immunization Practices for use of the Janssen (Johnson & Johnson) COVID-19 vaccine after reports of thrombosis with thrombocytopenia syndrome among vaccine recipients-United States, April 2021. *Morb Mortal Wkly Rep.* 2021;70(17):651. <https://doi.org/10.15585/mmwr.mm7017e4> PMID:33914723 PMCID:PMC8084127
39. Anderegg MA, Liu M, Saganas C, et al. De novo vasculitis after mRNA-1273 (Moderna) vaccination. *Kidney Int.* 2021;100(2):474-476. <https://doi.org/10.1016/j.kint.2021.05.016> PMID:34087251 PMCID:PMC8166777
40. Hernández AF, Calina D, Poulas K, Docea AO, Tsatsakis AM. Safety of COVID-19 vaccines administered in the EU: Should we be concerned? *Toxicol Reports.* 2021;8:871-879. <https://doi.org/10.1016/j.toxrep.2021.04.003> PMID:33898273 PMCID:PMC8055532
41. Tinari S, Riva C. Covid-19: Whatever happened to the Novavax vaccine? *bmj.* 2021;375. <https://doi.org/10.1136/bmj.n2965> PMID:34880071
42. Rossi AH, Ojeda DS, Varese A, et al. Sputnik V vaccine elicits seroconversion and neutralizing capacity to SARS-CoV-2 after a single dose. *Cell Reports Med.* 2021;2(8):100359. <https://doi.org/10.1016/j.xcrm.2021.100359> PMID:34308389 PMCID:PMC8266543
43. Tukhvatulin AI, Dolzhikova I V, Shchepochalov D V, et al. An open, non-randomised, 1/2 phase study on the safety, tolerability, and immunogenicity of single dose 'Sputnik light' vaccine for

- prevention of coronavirus infection in healthy adults. Published online 2021. <https://doi.org/10.2139/ssrn.3886430>
44. Tuhvatulin AI, Dolzhikova I V, Shcheblyakov D V, et al. An open, non-randomised, phase 1/2 trial on the safety, tolerability, and immunogenicity of single-dose vaccine "Sputnik Light" for prevention of coronavirus infection in healthy adults. *Lancet Reg Heal.* 2021;11:100241. <https://doi.org/10.1016/j.lanepe.2021.100241> PMID:34746910 PMCid:PMC8562788
45. Moore JP. Approaches for optimal use of different COVID-19 vaccines: issues of viral variants and vaccine efficacy. *Jama.* 2021;325(13):1251-1252. <https://doi.org/10.1001/jama.2021.3465> PMID:33662101
46. Klimek L, Chaker AM, Cuevas M, Becker S. COVID-19-Impfungen: replizierend oder nichtreplizierend? *Laryngo-Rhino-Otologie.* 2021;100(08):603-607. <https://doi.org/10.1055/a-1509-8916> PMID:34044465
47. Momin T, Kansagra K, Patel H et al. Safety and Immunogenicity of a DNA SARS-CoV-2 vaccine (ZyCoV-D): Results of an open-label, non-randomized phase I part of phase I/II clinical study by intradermal route in healthy subjects in India. *Eclinical Medicine.* 2021;38:101020. <https://doi.org/10.1016/j.eclinm.2021.101020> PMID:34308319 PMCid:PMC8285262
48. Vandenberg JI, Perry MD, Perrin MJ, Mann SA, Ke Y, Hill AP. hERG K<sup>+</sup> channels: structure, function, and clinical significance. *Physiol Rev.* 2012; 92(3):1393-478. <https://doi.org/10.1152/physrev.00036.2011> PMID:22988594
49. Schwartz PJ, Ackerman MJ. The long QT syndrome: a transatlantic clinical approach to diagnosis and therapy. *Eur Heart J.* 2013;34(40):3109-3116. <https://doi.org/10.1093/eurheartj/ehz089> PMID:23509228
50. Kapplinger JD, Tester DJ, Salisbury BA, et al. Spectrum and prevalence of mutations from the first 2,500 consecutive unrelated patients referred for the FAMILION® long QT syndrome genetic test. *Hear Rhythm.* 2009;6(9):1297-1303. <https://doi.org/10.1016/j.hrthm.2009.05.021> PMID:19716085 PMCid:PMC3049907
51. Zequn Z, Yujia W, Dingding Q, Jiangfang L. Off-label use of chloroquine, hydroxychloroquine, azithromycin and lopinavir/ritonavir in COVID-19 risks prolonging the QT interval by targeting the hERG channel. *Eur J Pharmacol.* 2021;893:173813. <https://doi.org/10.1016/j.ejphar.2020.173813> PMID:33345848 PMCid:PMC7746509
52. Albert RK, Schuller JL, Network CCR. Macrolide antibiotics and the risk of cardiac arrhythmias. *Am J Respir Crit Care Med.* 2014;189(10):1173-1180. <https://doi.org/10.1164/rccm.201402-0385CI> PMID:24707986 PMCid:PMC4061901
53. Chen N, Callaway CW, Guyette FX, et al. Arrest etiology among patients resuscitated from cardiac arrest. *Resuscitation.* 2018;130:33-40. <https://doi.org/10.1016/j.resuscitation.2018.06.024> PMID:29940296 PMCid:PMC6092216
54. Akhmerov A, Marbán E. COVID-19 and the heart. *Circ Res.* 2020;126(10):1443-1455. <https://doi.org/10.1161/CIRCRESAHA.120.317055> PMID:32252591
55. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* 2020;5(7):811-818. <https://doi.org/10.1001/jamacardio.2020.1017> PMID:32219356 PMCid:PMC7101506
56. Chen T, Wu DI, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *bmj.* 2020;368. <https://doi.org/10.1136/bmj.m1091> PMID:32217556 PMCid:PMC7190011