



Current trends in diagnosis and treatment strategies of COVID-19 infection

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Abstract

Coronaviruses are terrifically precise and adapted towards specialized respiratory epithelial cells, observed in organ culture and human volunteers both. This virus is found to possess an unpredictable anti-viral T-cell response which in turn results in T-cell activation and finally apoptosis, leading to cytokine storm and collapse of the whole immune system. The present review provides comprehensive information regarding SARS-CoV-2 infection, mutant strains, and the impact of SARS-COV-2 on vital organs, the pathophysiology of the disease, diagnostic tests available, and possible treatments. It also includes all the vaccines developed so far throughout the world to control this pandemic. Until now, 18 vaccines have been approved by the WHO and further 22 vaccines are in the third trial. This study also provides up-to-date information regarding the drugs repurposed in clinical trials and the recent status of allopathic drugs along with its result. Although vaccines are available, specific treatment is not available for the disease. Furthermore, the effect of vaccines on new variants is a new area of research at this time. Therefore, a preventive attitude is the best approach to fight against this virus.

Keywords SARS-CoV-2 · WHO · Vaccines · Pathophysiology · Treatment · Drugs

Abbreviations

ACE	angiotensin-converting enzyme
ANGPTL3	angiotensin-like protein 3
COVID-19	corona virus disease-19
FDA	Food and Drug Administration
FPV	Favipiravir
HIV	human immunodeficiency virus

MERS-CoV	Middle East Respiratory Syndrome-Coronavirus
MOA	mechanism of action
Mpro	main protease
RDV	remdesivir
RdRp	RNA-dependent RNA polymerase
RNA	ribonucleic acid
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
TCZ	tocilizumab
WHO	World Health Organization

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Introduction

December 2019 has been documented as a historic month for the emergence of the coronavirus disease also called viral pneumonia in Wuhan, China. This outbreak has propounded to approx. 220 countries, possessing more than 180,906,466 confirmed cases with 3,919,082 confirmed deaths and recovered cases 165,531,010 all over the world until the 25th of June 2021.

The virus was primarily cautiously named 2019 novel coronavirus (2019-nCoV). Consequently, the International Committee of Taxonomy of Viruses coined the name SARS-CoV-2, and so the disease was named COVID-19 (Zhou et al. 2020; Chen et al. 2020). This virus has been classified in genus, subgenus, and family: β -coronavirus, Sarbecovirus, and Coronaviridae respectively (Fig. 1) (Zhang et al. 2020a; Pottos et al. 2021).

SARS-CoV-2, extremely contagious and lethal, became an immense global health issue. As per the gene sequence analysis, SARS-CoV-2 is pertinent with two SARS-like coronaviruses observed in bats (approx. 88% resemblance) that possess rapid spreading characteristics all through the world. There are seven strains of coronavirus detected and identified which infect humans (HCoV), four of which are HCoV-229E, HCoV-NL63, HCoV-HKU1, and HCoV-OC43 that are common, seasonal, and liable to cause mild respiratory symptoms, whereas another two are zoonotic and virulent called MERS-CoV and SARS-CoV-1 and this SARS-CoV-2 possesses genetic similarity with SARS-CoV-1, both belonging to Sarbecovirus subgenus and β -coronavirus genus (Chen et al. 2020). Further study revealed that virus possesses envelope, +ve sense, single-strand of RNA linked with 30-kb genome (Arabi et al. 2020). It possesses proofreading machinery in order to reduce the mistakes during replication, therefore the mutations.

Research on SARS-CoV-2 revealed that it corresponds to Beta-coronavirus that possesses a characteristic genome structure as shown in Fig. 1. This virus is the biggest known RNA virus that has a specialty in possessing a replication-transcription system (RTS).

This also possesses 3'-5' exo-ribonuclease (some RNA-transforming enzymes with approx. 148 proteins). The mechanism of infection in a human cell has been illustrated in Fig. 2 (Cevik et al. 2020).

Decoding of genome results into structural (four proteins, i.e., spike, membrane, envelope, and nucleocapsid) as well non-structural proteins (for replicase transcriptase proteins). It binds to ACE2 receptors through spike protein for cell attachment and entry. The disease shows flu-like symptoms such as fever, cough, loss of taste, diarrhea, pneumonia, renal, asthenia, cardiac symptoms, and skin rashes. Happy hypoxia is also observed in COVID-19-positive cases which is also responsible for the causalities. In some situations, the patient also feels acute traumatic stress disorder, depression, and some psychological disorders, and few cases commit suicide also due to it (Markham and Keam 2018). The effect of SARS Cov-2 on various vital organs is shown in Fig. 3.

Coronavirus strains

The coronavirus term implies a huge virus's family known since a long time ago. Before this pandemic, many coronaviruses are known to infect humans and cause mild respiratory illnesses such as cough and colds. This novel COVID-19 virus is not new to us but it is very rare that a virus jumps from animals/plants to humans and causes disease. This happens with the COVID-19 virus; therefore, it infects humans rapidly, due to its extreme contagious nature (Jena 2021; Jha et al. 2021; Jin et al. 2020; Shahab et al. 2021, Huang et al. 2020). Variants known to date are compiled in Table 1.

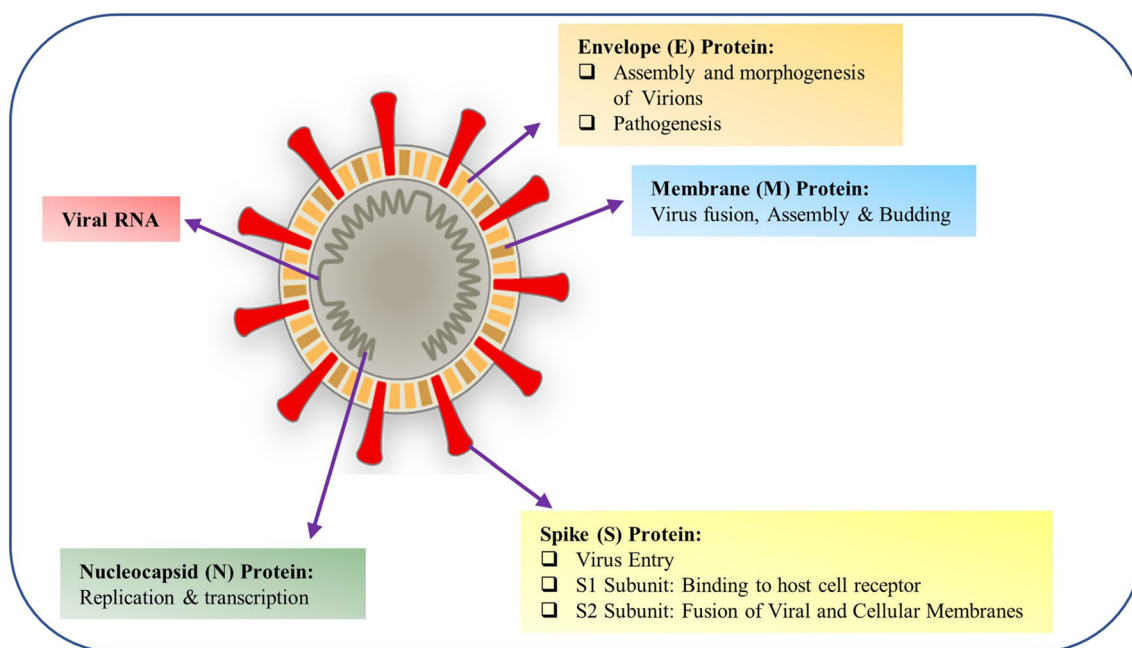


Fig. 1 Structure of SARS-CoV-2 virus

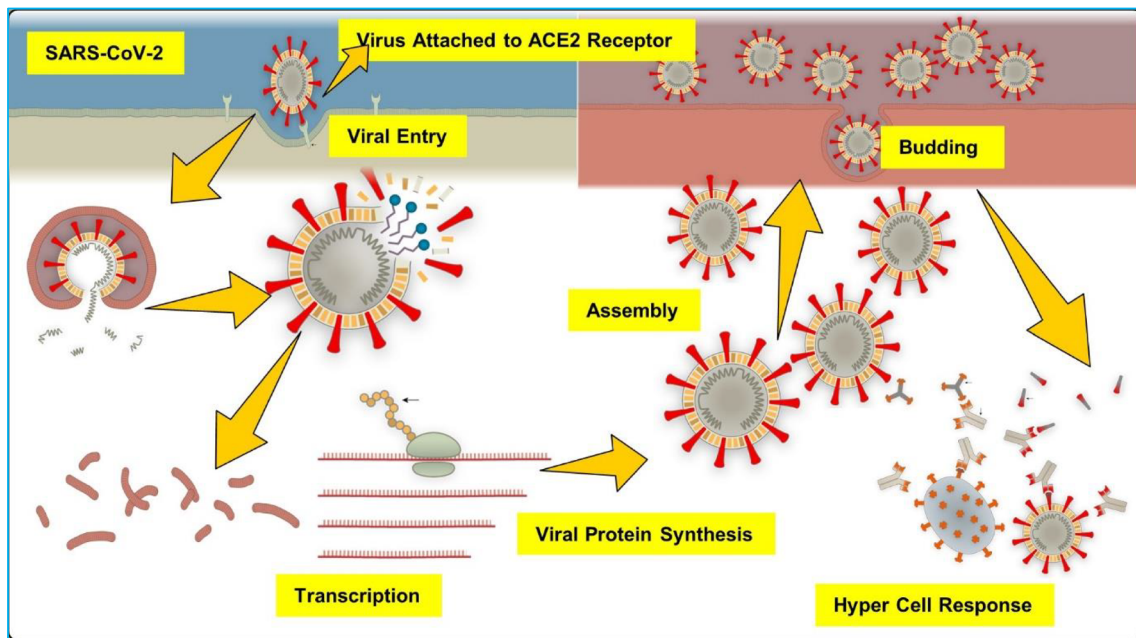


Fig. 2 Mode of infection of SARS-CoV-2 in human cell

Mutations

It is well known that viruses are the link between living and non-living organisms as they do not contain any cells. Therefore, there are more chances of mutations in viruses during human infection as well as disease progressions as the simplest structure. Most of the mutations are harmful to the organisms but few may be beneficial too. As a result of mutations, these viruses

may appear in a little bit different form and can cause the disease in an extreme contagious manner as shown in the case of the COVID-19 virus.

D614G was found to be the first variant that has been observed near late January or early February 2019 and replaced the original strain somewhere in June 2020 which became dominant and spread throughout the world. The enhanced infectivity and transmission have been observed without a change in the severity of the disease.

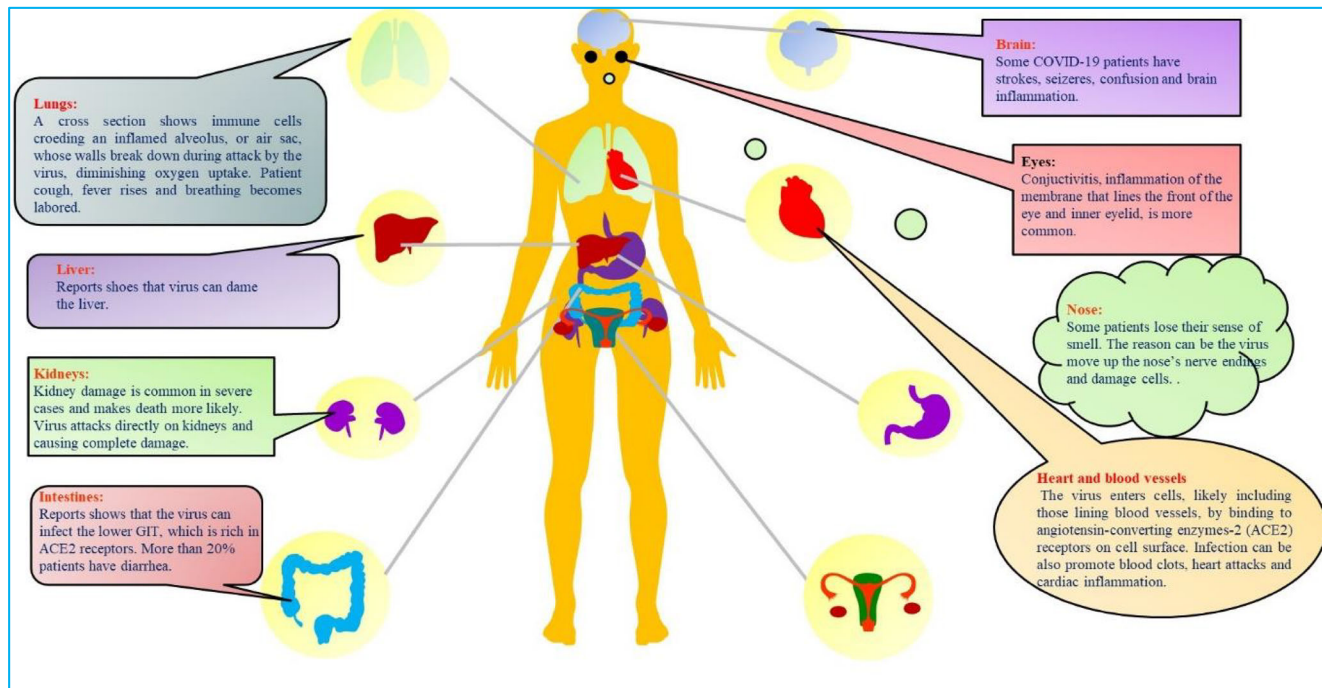


Fig. 3 Effect of SARS COV-2 on vital organs

Table 1 Different variants of COVID-19

Origin nation	New name	Variant/lineage	Ref.
USA	Iota (ι)	B.1.526	Shahab et al. (2021)
New York	Epsilon (ϵ)	B.1.427/429	
South California			
Philippines	Theta (θ)	P.3	Shahab et al. (2021)
Brazil	Gamma (γ); Zeta (ζ)	P.1; P.2	Shahab et al. (2021)
India	Delta (δ); Kappa (κ)	B.1617.2; B.1617.1	Shahab et al. (2021)
UK	Alpha (α)	B.1.1.7	Shahab et al. (2021)
South Africa	Beta (β)	B.1.351	Shahab et al. (2021)
Other countries	Eta (η)	B.1.525	Shahab et al. (2021)

Cluster 5, another mutant, has been observed somewhere between August and September 2020 through Danish personnel infected by framed mink which later jumped to humans. As the name suggests, Cluster 5 is an aggregate of strains, observed in 12 persons until now, not found to spread extensively. SARS-CoV-2 VOC 202012/01 (mutant of interest) has been reported by UK personnel to the WHO (December 14, 2020). This mutant possesses 23 nucleotide changes found to be not related phylogenetically to the SARS-CoV-2 virus, the main cause of coronavirus disease at that time. Due to the above substitutions, this strain was found to possess enhanced transmissibility without any change in disease severity (Ruan et al. 2020). The variants that are known and the different mutants along with the site of mutations are summarized in Table 2.

Triple COVID-19 mutation

Triple mutation in COVID-19 has also been observed in few parts of Delhi, West Bengal, and Maharashtra. Mutations at sites 452 and 484 have been reported individually; for example, in California, variants B.1.427 and B.1.429 have the L452R mutation. E484K has been seen in the variants reported from the UK, South Africa, and Brazil. Mutations at site

P681 have also been seen in some lineages before as well as the mutation E484Q. The combination of all the three mutations reported here, L452R, E484Q, and P681R, suggests the virus emerging similar traits autonomously, continually adapting to its human hosts (Perrella et al. 2020; Del Rio et al. 2020).

Pathogenesis of disease

When a virus enters in body through the nose or mouth, it stays near the paranasal cavity and tries to make colonies, which results in headache and loss of smell and taste at the very first level. After 24–36 h, it invades the respiratory and gastrointestinal system and causes abdominal pain and loss of motion. The body defense system activates, and macrophages accumulate at the site and try to engulf the virus and send the messages in a form of IL-1, IL-6, and TNF to other body cells as well as neutrophils to be active against infection.

By the examining IL-6 level, we can make an idea regarding the body's preparation against the virus. As the disease progresses, further neutrophils accumulate and try to kill the virus, but body cells will also be affected. At 5–6 days of the disease, chances of cytokine storm occur due to over responsiveness of the body. The virus attacks on type 2

Table 2 Different mutant along with site of SARS-COVID-2

Variants	Mutation		Ref.
	Type	Site	
B.1.617	E484Q, L452R and P681R	Spike protein	Shahab et al. (2021)
20H/501Y.V2 or B.1.351)	K417N, E484K and N501Y	Whole genomes and spike protein	Shahab et al. (2021)
CAL.20C or B.1.427/429	L452R mutation	Spike protein	Shahab et al. (2021)
P.1/P2 or B.1.1.28	K417N/T, E484K, N501Y	Spike protein	Shahab et al. (2021)
A.23.1	F157L, V367F, Q613H and P681R	Spike protein	Shahab et al. (2021)
20I/501Y.V1, VOC 202012/01, or B.1.1.7	N501Y, P681H E484K	Spike protein	Shahab et al. (2021)

pneumocytes, which secretes some surfactants and helps in lung expansion during respiration. Another target for the virus is the liver and kidney. Macrophage activates the liver to produce a c-reactive protein which gives signals to other parts of the body to be overreactive against infection (Jain 2020).

These signals can also act on the liver to produce and release fibrinogen which when reacts with platelets forming unnecessary clots in the body which floats in the blood and can block any artery/vein that may result in pulmonary embolism, heart attack, and stroke. These blood clots can be examined by testing the level of d-dimer. When an infection invades the heart cells, it releases HSCRP which causes damage to the cardiac muscle cells. Cytokines can activate the thermo regulators in the hypothalamus and result in fever. The liver function and cell damage can be checked by examining SGOT, SGPT, blood level. Cell damage can be checked through LDH level and a patient's life can be saved by taking therapy on time (Favalli et al. 2020).

Once SARS-CoV-2 enters the alveolus, it begins to infect type II alveolar cells and replicate. The infected type II alveolar cells release pro-inflammatory cytokines, which signal the immune system to respond. Patients may experience mild symptoms, such as cough, fever, and body aches. Macrophages release IL-1, IL-6, and TNF- α . IL-6, causing vasodilation and allowing more immune cells to travel to the alveolus. It also increases capillary permeability, causing plasma to leak into the interstitial space and the alveolus. Neutrophils release reactive oxygen species and proteinases, which destroy infected cells. These dead cells combine with the plasma to form a protein-rich fluid that accumulates within the alveolus, causing shortness of breath and pneumonia. Accumulation of fluid and dilution of surfactant lining of the alveolus cause alveolar collapse, which decreases gas exchange and can lead to hypoxemia and acute respiratory distress syndrome. If the immune system goes into overdrive, inflammation can spread throughout the circulatory system, leading to systemic inflammatory response syndrome, also known as a cytokine storm. This systemic inflammation can cause septic shock, where blood pressure drops dangerously low and organs can no longer be perfused, leading to multi-organ failure and death.

COVID-19-related comorbidities

As explained in the preceding sections, the SARS-Cov-2 virus has undergone numerous changes, resulting in more dangerous variants. In type 2 asthmatic individuals, COVID-19 infection becomes more severe. They also outline the treatment options and medications that can be utilized to address mild, moderate, and severe COVID-19 symptoms in asthmatic patients, preventing aggravation. The progressive results were highly contradictory, as severe cases of COVID-19 showed an increase in the levels of numerous cytokines that might

exacerbate bronchial tract inflammation, exacerbating asthma attacks. Contrary to popular belief, certain data show that COVID-19 severity is reduced in type 2 asthmatic patients with elevated T-cells, since most COVID-19 positive individuals have a significant drop in T-cells. This helps to restore the balance of immunological responses, slowing the advancement of the disease (Ghosh et al. 2021).

Obesity stimulates the development of gene-induced hypoxia and adipogenesis in obese mice. Obesity increases the likelihood of developing immune-mediated and certain inflammatory-mediated illnesses, such as atherosclerosis and psoriasis, by dampening the immunological response to infectious pathogens, resulting in weakened post-infection effects. Furthermore, the obese host produces a unique milieu for disease development, characterized by low-grade inflammation that persists. To protect our bodies and reduce the danger of infectious illnesses, including COVID-19, it is recommended to maintain good eating habits by increasing the intake of diverse plant-based and low-fat meals (Behl et al. 2020).

The virus appears to enter the CNS mainly via the angiotensin-converting enzyme-2 (ACE-2) receptor and nasal route through the olfactory bulb and cribriform plate and propagates through trans-synaptic signaling, and moves retrogradely into the CNS along the nerve fiber, according to evidence. Parkinsonism, Alzheimer's disease, meningitis, encephalopathy, anosmia, hyposmia, anxiety, sadness, psychiatric symptoms, seizures, stroke, and other problems have been linked to viral invasion of the CNS. As a consequence, even after the individual has cured from COVID-19, the COVID-19 CNS components should be checked on a regular basis to prevent long-term CNS issues (Nagu et al. 2020).

Diagnosis

Recently, two types of tests have been performed for the diagnosis:

- a. Molecular tests
- b. Antigen tests.

Molecular test detects viral genome whereas antigen tests target characteristic viral proteins.

Antibody test targets the antibodies that have been produced in patient's blood with response to viral infection but it can be detected in post-COVID-19 patients also (Shahab et al. 2021; Ojha et al. 2021; Shoaib et al. 2021). Diagnostic tests are compiled in Table 3 and Fig. 4.

Drugs used in the management of SARS COV-2 infection

The repurposed drugs used in the management of SARS COV-2 infections (Pawelczyk and Zaprutko 2020; Parasher

2021; Saxena 2020; Gil et al. 2020) are listed and compiled in Table 4. Different drugs along with the mechanism of action in the management of SARS COV-2 are shown in Fig. 5.

Mechanism of action of drugs for the treatment of SARS-COV-2

Chloroquine/hydroxychloroquine

The mechanism of chloroquine and hydroxyl-chloroquine drugs involves the conversion of chloroquine to hydroxychloroquine which in turn inhibits several enzymes. Due to enzyme inhibition, viral entry is inhibited due to these weak bases because of pH dependency. The drug also inhibits glycosyl-transferases and post-translation modifications and also inhibits viral families. The mechanism of action is depicted in Fig.6 (Schrezenmeier and Dörme 2020).

Favipiravir

Favipiravir is an approved drug employed for severe influenza virus infection in China. It is available in an inactive form and gets converted into an active form by the action of enzymes into favipiravir ribo-furanosyl monophosphate (RMP) which

further converts into the active form (favipiravir ribo-furanosyl triphosphate) which in turn can block the replication of several RNA viruses currently in clinical trials in COVID-19 management. The mechanism of action has been presented in Fig. 7 (Sood et al. 2021).

Remdesivir

It is a broad-spectrum antiviral drug; adenosine analog that can determine pre-mature termination of viral RNA. It has been tested for Ebola virus infection and might be useful in the treatment of other RNA virus infections. It has been shown that the action against SARS COV-2 infection also, still, studies are going on and showed in Fig. 8 (Beigel et al. 2019; Wang et al. 2020a).

Monoclonal antibodies

Monoclonal antibodies can be produced by immunizing the rats with antigens but sometimes failed to secrete antibodies. This can be further modified by mixing the myeloma cells with plasma cells from the spleen. Cell fusion results in hybridomas cells, which are transferred to hat medium and incubated. Hybridomas cells are further selected which produced antibodies known as monoclonal

Table 3 Diagnostic tests for SARCOV-2

Test	Principle	Sample	Advantage/cost	Ref.
Enzyme-linked immunosorbent assay	The antibody binds with coated antigen in ELISA plates results in forming the complex and labelled secondary antibody can be detected by colour/ fluorescence.	Serum/plasma	Rapid Not very Expensive	Nguyen et al. (2020); Li and Xia (2019)
Chemiluminescence immunoassay	Uses chemical probes that would emit light through a chemical in order to label the antibody for COVID-19.	Blood serum/-plasma	Sensitive Rapid Expensive	Nguyen et al. (2020), Li and Xia (2019)
COVID antigen assay	COVID-19 can be detected against specific antibody-based tests like ELISA/CLIA	Blood serum /plasma	Rapid Variable costs	Nguyen et al. (2020), Li and Xia (2019)
RT-PCR	RNA of COVID-19 can be converted to cDNA through transcriptase enzyme can be followed via real-time PCR for augmentation of cDNA	Upper respiratory	Gold standard assessment, sensitive Expensive	Nguyen et al. (2020), Li and Xia (2019)
RT-LAMP	Conversion of RNA of COVID-19 to cDNA via transcriptase enzyme and is performed at a temperature between 60 and 65 °C.	Upper respiratory specimens	Does not need thermal cyclers, time-efficient, high-tech labs are not required. Very cost-effective	Nguyen et al. (2020), Li and Xia (2019)
Nucleic acid hybridization technique	Translation of RNA of COVID-19 to cDNA through transcriptase enzyme further mixing in wells with fixed COVID-19-specific oligonucleotides followed by washing hybridized virus cDNA emits signal indicates positive results.	Upper respiratory	Sensitive Expensive	Nguyen et al. (2020), Li and Xia (2019)

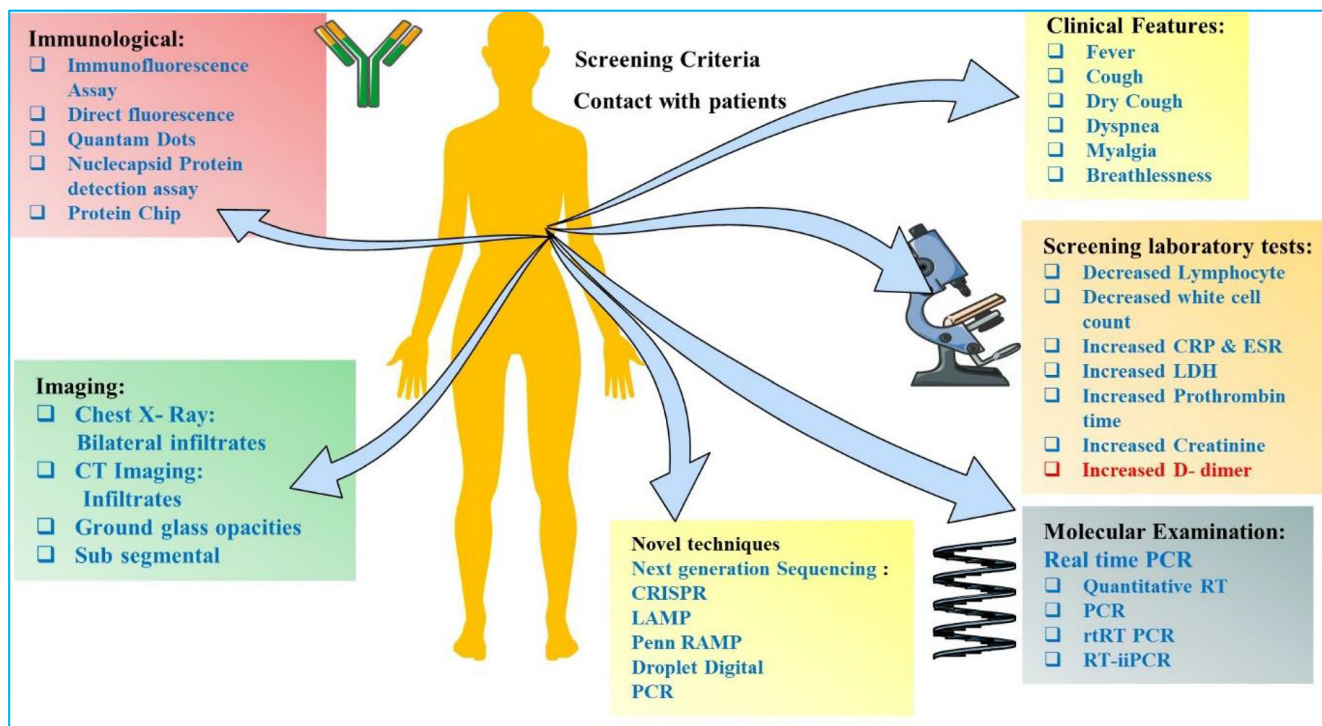


Fig. 4 Diagnostic tests employed for SARS COV-2

antibodies. These antibodies are found to be effective against COVID-19 and came in light when given to the ex-US president Donald Trump. The monoclonal antibody cocktail is a combination of two or more monoclonal antibodies which is administered to the patient as a single dose. These are found to exhibit activity by acting on the spike protein of the COVID-19 and do not allow it to enter into the human cell. For the treatment of mild to moderate covid infection, the combination of Bamlanivimab (700mg) and the mixture of Casirivimab and Imdevimab (2400mg) appeared to accelerate decline SARS-COV-2 level compared to placebo. Casirivimab and Imdevimab are mainly human immunoglobulin G-1 (IgG1). Figure 9 describes a method of production of monoclonal antibodies (Richardson et al. 2020; Ceribelli et al. 2020; Marovich et al. 2020; Zost et al. 2020; Goyal et al. 2021; Yang et al. 2020; Clinical Trial Arena 2020; Phan et al. 2021).

Recently, Zydus claimed regarding the repurposing of “Virafin” (pegylated interferon alpha-2b) in COVID-19 treatment which was earlier used in the treatment of the hepatitis C virus. Recently, Virafin has been given limited emergency approval from DCGI, India (Science The Wire 2021).

One more drug named “2-DG” has been developed by DRDO along with Dr. Reddy’s Lab. Hyderabad has been granted emergency approval from DCGI, India as an adjunct therapy to overcome oxygen demand. This drug has been developed in the treatment of cancer as it possesses promising cytotoxic potential (Economic times. Indiatimes 2021).

Currently, Canadian company *Sanotize* developed nitric oxide-based nasal spray, claimed to kill COVID-19 load inside the nose up to 99.99 %. Now, the company has filed for getting emergency approval in the UK and started its production in Israel (India today 2021).

Approved and phase 3 trial vaccines

Vaccines are the hope for controlling this pandemic caused by the COVID-19 virus. Few vaccines have been approved by regulatory authorization whereas some of them are in the process. It should be very clear that no vaccine is 100% effective until now; still results will prove the efficacy and safety of the vaccines. Each and every person must follow the guidelines and hygienic conditions. Scientists all over the world are working at war level for the production of vaccines; until now, 79 vaccines are still in process and among them, 11 vaccines have been approved by regulatory authorities whereas 20 vaccines are still in phase III clinical trials (Li and De Clercq 2020; Li et al, 2020a; Zoomer 2021; Graham, 2020) Vaccines that have been approved by regulatory authorities until now are shown in Table 5. The list of approved vaccines in phase trial 3 is compiled in Table 6.

Nano-medicines in SARS Cov-2 infection

Nano-technology possesses enormous potential in targeted drug delivery at the target site with minimum side effects,

Table 4 Repurposed drugs used in the management of SARS COV-2

Groups	Drugs	Applications	Results related to COVID-19	Ref.
.Antivirals	Baloxavir	Antiviral active against influenza viruses Conflicting data regarding possible in vitro antiviral activity against SARS-CoV-2	Although investigated as a potential treatment during the early stages of the COVID-19 pandemic, 1, 6, 7 in vitro antiviral activity against SARS-CoV-2 was not confirmed and there are no data to support the use of baloxavir in the treatment of COVID-19.	Lou et al. (2021); Li and De Clercq (2020); Li et al. 2020a
	Remdesivir (RDV)	Nucleotide analog prodrug; RNA polymerase inhibitor. In vitro evidence of activity against SARS-CoV-2 in Vero E6 cells.	Accelerating the patient's recovery, having no specific side effects	Beigel et al. (2019); Wang et al. (2020a); Agostini et al. (2018)
	Favipiravir (FPV)	Influenza	Accelerating the patient's recovery, having few side effects	Sood et al. (2021); Wang et al. (2020b); Dong et al. (2020a); Furuta et al. (2017)
	Umifenovir	Broad-spectrum antiviral with in vitro activity against various viruses, including coronaviruses. Although data is limited, in vitro activity against SARS-CoV-1 4 and SARS-CoV-2 5 reported.	No significant treatment effect in COVID-19.	LianN et al. (2020); Dong et al. (2020a)
Neuraminidase inhibitors	Oseltamivir	Oseltamivir did not demonstrate in vitro antiviral activity against SARS-CoV-2 in Vero E6 cells	No Evidence in the treatment of SARS-CoV-2	Chen et al. (2020); Lu (2020)
Serine protease inhibitors	Nafamostat and Camostat	Both the drugs were found to block the entry of SARS-COV-2 into cells	In phase 2 and phase2/3 clinical trial	
HIV Protease Inhibitors	Lopinavir and Ritonavir	Works via inhibition of 3-chymotrypsin like protease.	When both the drugs are given in combination, reduced time to alleviation of symptoms and reduced hospital stay.	Recovery Collaborative group (2020); Chu CM et al. (2004)
	Atazanavir (ATV)	Some evidence that ATV alone or with ritonavir (ATV/RTV) has in vitro activity against SARS-CoV-2 in Vero E6	Initially noted that it reducing the disease symptoms, not accelerating the disease treatment, increasing the risk of bradycardia, but later on, the manufacturer states they have no clinical or pharmacologic evidence to support use for the treatment of COVID-19.	
Antibiotics	Other HIV protease inhibitor drugs (Nelfinavir, Ritonavir, Saquinavir, and Tipranavir)	Some evidence of in vitro activity against SARS-CoV-2 in Vero cells	Still not potent evidence of drugs in the treatment of SARS-Cov-2	
	Azithromycin	Some evidence of in vitro activity against SARS-CoV-2 in infected Vero E6 and Caco-2 cells; clinical importance unclear.	Only limited information available regarding the frequency and microbiology of bacterial pulmonary coinfections or superinfections in pts with COVID-19	Tran et al. (2019); Bermejo-Martin et al. (2009)
	Teicoplanin	Ebola	Having inhibitory effects on viral infection	
Monoclonal Antibodies	Baricitinib	Inflammatory diseases, rheumatoid Arthritis, Used in	Reducing inflammatory responses, having a greater	Richardson et al. (2020); Ceribelli et al. (2020);

Table 4 (continued)

Groups	Drugs	Applications	Results related to COVID-19	Ref.
		the management of hyperinflammation resulting from viral infections such as COVID-19	efficiency in combination with RDV and LPV-RTV, having the possibility of creating anemia	Marovich et al. (2020); Zost et al. (2020); Myron (2021); Favalli et al. (2020)
	Bemcentinib	It was well known to reveal the potent anti-viral potential in preclinical studies against Ebola and Zika virus besides other viruses. Recently in the repurposing of drugs also includes it for further research on possible treatments of coronavirus disease.	Bemcentinib (AXL kinase suppressor) prevents entry of virus to the cell as well as also inhibits type 1 interferon, supporting its use in SARS-CoV-2	Goyal et al. (2021)
	Bevacizumab	The brand name of the drug is Avastin prescribed for cancer treatment also repurposed in search of possible covid-19 treatment prescribed for 20 patients in China (Shandong University, Jinan, Qilu hospital). Currently in the second and third phases of clinical trials.	This drug act as a human monoclonal antibody which predominantly targets vascular endothelial growth factor results in depletion of VEGF which in turn produce hypoxia, over-expression of respiratory epithelium, critical inflammation which in combination may conquer edema in COVID-19 patients.	Wang et al. (2004)
	Leronlimab	FDA provides eIND acceptance for use in severe/critical COVID-19 persons under the name of Vyrologix™ (leronlimab).	It acts as aCCR5 antagonist reported to inhibiting “cytokine storm” in severely infected patients studied in New York.	IntradoGlobeNewswire (2020); Yang et al. (2020)
	Bamlanivimab (LY-CoV555) and Etesevimab (LY-CoV016)	Bamlanivimab and Etesevimab together for the treatment of COVID-19	FDA issued an Emergency Use Authorization (EUA) for Bamlanivimab and Etesevimab on February 9, 2021, that permits	Clinical Trial Arena (2020)
	Casirivimab and Imdevimab (REGN10933 and REGN10987; REGN-COV®)	This combination has been received FDA emergency use approval for the treatment of early Covid-19 infection.	This combination of antibodies is planned especially to stop the infection of the covid-19 virus. It was granted FDA Emergency Use Authorization on November 21, 2020, for the treatment of mild to moderate COVID-19.	Phan et al. (2021); Fda.gov (2021)
Interferons	IFN beta1a, IFN beta-1b, IFN beta-1a	Interferons (IFNs) modulate immune responses to some viral infections	Efficacy and safety of IFNs for treatment or prevention of COVID-19 not established.	Mantlo et al. (2020); Sallard et al. (2020)
Interleukin-6	Tocilizumab (TCZ)	Recombinant humanized monoclonal antibody specific for the interleukin-6(IL-6) receptor; IL-6 is a proinflammatory cytokine. Tocilizumab may potentially combat cytokine release syndrome (CRS) and pulmonary symptoms in severely ill COVID-19 patients	Showing significant clinical progress, reducing inflammatory markers, reducing mortality, reducing the risk of invasive mechanical ventilation, improving oxygen delivery in patients, having few side effects	Salama et al. (2021); Lu (2020); Luo et al. (2020); Zhang et al. (2020b)
	Sarilumab (Kevzara®)	Recombinant humanized monoclonal antibody specific for the interleukin-6(IL-6) receptor; IL-6 is a proinflammatory cytokine. Sarilumab may potentially combat	There are insufficient data for the Panel to recommend either for or against the use of sarilumab for hospitalized patients with COVID-19	National Health Commission and State Administration of Traditional Chinese Medicine (2020)

Table 4 (continued)

Groups	Drugs	Applications	Results related to COVID-19	Ref.
		cytokine release syndrome (CRS) and pulmonary symptoms in severely ill patients		
	Siltuximab (Sylvant®)	A recombinant chimeric monoclonal antibody specific for the interleukin-6(IL-6) receptor; may potentially combat cytokine release syndrome (CRS) symptoms (e.g., fever, organ failure, death) in severely ill patients	Efficacy and safety of siltuximab in the treatment of COVID-19 not established	Ceribelli et al. (2020); Zhang et al. (2020a)
	Ruxolitinib (Jakafi®)	Janus kinase (JAK) inhibitor; may potentially combat cytokine release syndrome (CRS) in severely ill patients	Recommended against the use of JAK inhibitors other than Baricitinib	U.S. National Library of Medicine (2021)
Corticosteroids (CSs)	Dexamethasone	As per the trials conducted in the UK, Dexamethasone decreases mortality to some extent too but it is not effective in acute and mild infection infect worsen the condition. Side effects of corticosteroids should also be taken into consideration before prescribing the drug.	The severe COVID-19 positive patients experience hyper-inflammatory response results in cytokine storm which ultimately results in a condition called hemo-phagocytic lymphohistiocytosis. Immunosuppressive agents will be helpful for the patient. Therefore, it might be effective for severe infection. On the contrary, in acute or mild infection cases this can worsen the symptoms by suppressing the immune system.	Veronese et al. (2020); Russell et al. (2020); Griffiths et al. (2019); Siemieniuk et al. (2015)
	Methyl-prednisolone	These corticosteroids may be beneficial in severely/critically infected patients but they should be taken precautiously due to side effects.	A widely used glucocorticoid called methyl-prednisolone is being studied for safety and effectiveness in the treatment of novel coronavirus pneumonia in a number of hospitals in the Hubei province of China.	Wang et al. (2020b)
Recombinant human	interleukin-1(IL-1) receptor antagonist	Anakinra (Kineret®)	There are case study data but no known published prospective clinical trial evidence supporting efficacy or safety of anakinra for treatment of COVID-19	NIH COVID-19 Treatment Guidelines Panel states that there are insufficient clinical data to recommend either for or against the use of anakinra in the treatment of COVID-19
Aouba et al. (2020); Huet et al. (2020)				
Anticoagulants	Heparin	Coagulation problems	Reducing mortality, having side effects including drug resistance and heparin-induced thrombocytopenia (HIT)	Deng et al. (2020b); Li et al. (2020b); Carfora V et al. (2021)
	Warfarin	Coagulation problems	Having the ability for in vitro inhibition of SARS-CoV-2 S protein-mediated cell fusion.	
ACE Inhibitors, Angiotensin II	ACE inhibitors may have a protective effect against lung damage or may have a	Patients with cardiovascular disease are at an increased risk of severe COVID-19. It	The panel recommends against the use of ACE inhibitors or ARBs for the treatment of	Fang et al. (2020); Bozkurt et al. (2020)

Table 4 (continued)

Groups	Drugs	Applications	Results related to COVID-19	Ref.
Receptor Blockers	paradoxical effect in terms of virus binding.	is unclear whether use of ACE inhibitors or ARBs has a positive or negative impact on the treatment and clinical outcomes of COVID-19.	COVID-19 except in the context of a clinical trial.	
Antiparasitic	Ivermectin	Early usage of Ivermectin in acute, mild Covid-19 positive patients. The results found in pilot study make the basis for the early management of COVID-19. It may be beneficial for prophylaxis also in high-risk areas.	It may act via various antiviral mechanisms. One mechanism might be positive allosteric inflection of receptors through Ivermectin leads to ACE-2 receptor down-regulation results in hindering the viral entry within the cell respiratory and olfactory bulb. It may also act via inhibiting pro-inflammatory pathways in the olfactory bulb which in turn plays a major role in anosmia development in COVID-19 infection. The drug is also known to inhibit pro-inflammatory genes (IL-8, TNF-a, etc.).	Chaccour et al. (2021); Caly et al. (2020); Mastrangelo et al. (2012)
Antiprotozoal	Nitazoxanide (Alinia®)	Some in vitro evidence of potential synergism between nitazoxanide and remdesivir and between nitazoxanide and umifenovir against SARS-CoV-2; additional data needed	NIH COVID-19 Treatment Guidelines Panel recommends against the use of any agents for postexposure prophylaxis for prevention of SARS-CoV-2 infection, except in a clinical trial	Wang et al. (2020a); Beigel et al. (2019)
Anthelmintic	Niclosamide	In drug repurposing screens, niclosamide was found to inhibit replication of SARS-CoV-2 in vitro in Vero E6 cells	Not commercially available in the US. Although suggested as a potential treatment for COVID-19 based on its broad antiviral activity, including in vitro activity against coronaviruses.	Wu et al. (2004); Xu et al. (2020)
.Nonsteroidal	anti-inflammatory agents	Paracetamol		WHO recommending paracetamol
	Fang et al. (2020); Alhazzani et al. (2021)	Ibuprofen	The speculative link between ibuprofen and increased ACE2 expression, which possibly could lead to worse outcomes in COVID-19 patients	Concerns that anti-inflammatory drugs such as ibuprofen may worsen COVID-19 circulated widely in the early months of the pandemic
Indomethacin		In vitro antiviral activity in SARS-CoV-2 pseudo virus–infected Vero E6 cells	Additional data is needed to determine whether in vitro activity against SARS-CoV-2 corresponds with clinical efficacy in the treatment of COVID-19.	
Thrombolytic agents	t-PA (Alteplase, Tenecteplase	Fibrinolysis shutdown, as evidenced by the complete failure of clot lysis on thromboelastography, has been observed in critically ill patients with COVID-19	t-PA has been proposed as a salvage treatment for COVID-19 patients (e.g., those with decompensating respiratory function who are not responding to or do not have access to mechanical	Moore et al. (2020); Deng et al. (2020b)

Table 4 (continued)

Groups	Drugs	Applications	Results related to COVID-19	Ref.
Immunoglobulin	Commercially available immune globulin (nonSARS-CoV-2-specific IGIV, IVIG, γ -globulin)		ventilation or extracorporeal membrane oxygenation The role of commercially available immune globulin (non-SARS-CoV-2-specific IGIV) and investigational anti-SARS-CoV-2 hyperimmune globulin (anti-SARS-CoV-2 hIGIV) in the treatment of COVID-19 is unclear.	Jawhara (2020); Sanders et al. (2020)
Antilipemic Agents	HMG-CoA Reductase Inhibitors (statins)	Statins affect ACE2 as part of their function in reducing endothelial dysfunction	Recommends against the use of statins for the treatment of COVID-19	Phadke and Saunik (2020); Frost et al. (2007)
Antidepressant	Fluvoxamine (Luvox CR®) (Selective Serotonin reuptake Inhibitors)	Fluvoxamine is an antidepressant with a high affinity at the sigma-1 receptor, which potentially could help prevent clinical deterioration in patients with COVID-19.	There are insufficient data to recommend either for or against the use of fluvoxamine for the treatment of COVID-19.	Hashimoto (2021); Rosen et al. (2019)
Histamine H2 antagonists	Famotidine	No in vitro antiviral activity against SARS-CoV-2 was observed in infected Vero E6 cells.	Safety and efficacy for treatment of COVID-19 Not established.	Wu et al. (2020); Dong et al. (2020b)
Vitamin D	Vitamin D receptor is expressed on immune cells (e.g., B cells, T cells, antigen-presenting cells); these cells can synthesize and respond to active vitamin D.	Only limited prospective clinical trial evidence regarding the efficacy of vitamin D supplementation for treatment or prevention of COVID-19.	Efficacy of vitamin D supplementation in the prevention or treatment of COVID-19 has not been established.	Martineau AR et al. (2017)
Zinc	Trace minerals involved in immune function, including antibody and white blood cell production; an important cofactor for many enzymes; may improve wound healing.	No evidence from controlled trials that zinc is effective in the prevention or treatment of COVID-19.	It remains unclear whether zinc supplementation is beneficial in the prophylaxis and/or treatment of COVID-19; further study is needed.	Bauer et al. (2020); McCarty and DiNicolantonio (2020)
COVID-19 Convalescent Plasma	Convalescent plasma therapy has been used in the treatment of other viral diseases with various degrees of success.	Plasma obtained from patients who have recovered from COVID-19 (i.e., COVID-19 convalescent plasma) that contains antibodies against SARS-CoV-2 may provide short-term passive immunity to the virus; theoretically, such immunity may prevent or contribute to recovery from the infection, possibly as the result of viral neutralization and/or other mechanisms.	Efficacy and safety of COVID-19 convalescent plasma for the treatment of COVID-19 not established.	Bloch et al. (2020); Tiberghien et al. (2020)
Nebulized drugs	Albuterol	nebulized drugs for the management of respiratory conditions in patients with COVID-19 infection may distribute the virus into the air and expose close contacts	There is a lack of published information and guidance on the optimal administration of aerosolized drugs in the treatment of patients with COVID-19. The safe and effective delivery of aerosol therapy to such patients may require modifications in dosage, frequency, and	Simonds et al. (2010)

Table 4 (continued)

Groups	Drugs	Applications	Results related to COVID-19	Ref.
Vasodilating agent	Nitric oxide (inhaled)	Selective pulmonary vasodilator with bronchodilatory and vasodilatory effects in addition to other systemic effects mediated through cGMP-dependent or independent mechanisms; may be useful for supportive treatment of acute respiratory distress syndrome (ARDS), a complication of COVID-19	delivery techniques, as well as the use of protective measures. Recommended against the routine use of inhaled nitric oxide in mechanically ventilated adults with COVID19	Akerstrom et al. (2005); Chen et al. (2004)
	Inhaled prostacyclins (e.g., eprostenol, iloprost)	Selective pulmonary vasodilators; may be useful in the adjunctive treatment of acute respiratory distress syndrome (ARDS), a complication of COVID-19	It may be considered as rescue therapy in mechanically ventilated adults with COVID-19	Cherian et al. (2018)
Miscellaneous drugs	Colchicine	The use of has been reported in the treatment of COVID-19 disease through some case studies performed in covid-19 positive patients. The treatment would possibly decrease a person's morbidity/mortality, support to avoid hospital admission, and therefore can reduce the care cost for patients.	Being an anticancer drug also possesses anti-inflammatory potential via inhibiting NLRP 3 inflammasome leads to inhibit the cytokine production or cytokine storm is the major cause of inflammation in COVID-19 infection. Apart from it possesses a pleotropic mechanism, not possessing immunosuppressive potential, cheap, and does not augment the infection risk.	Reyes et al. (2020); Deftereos et al. (2020); Gandolfini et al. (2020)
	Chloroquine, Hydroxy chloroquine (CQ/ HCQ)	Viral and autoimmune diseases	Effectively controlling the disease with or without azithromycin, reducing mortality. However, the efficacy and safety of chloroquine for treatment or prevention of COVID-19 not established.	Schrezenmeier and Dörne (2020); Wang et al. (2020a)
	Quinacrine	It is found to be anti-SARS-CoV-2 drug, recently reported to possess anti-SARS-COV-2 potential	This drug may interfere with the SARS-CoV-2 RNA, may hamper both transcription and translation. It also increases the pH of endosomes/lysosomes results in protease inhibition and fusion with auto-phagosomes thus results in inhibition of viral release and enhance auto-phagolysosomes.	Pineda et al. (2021)

especially in the anticancer domain. This technology has been extensively utilized in the development of vaccines against the COVID-19 virus.

Viruses can be categorized as nanoparticles, which work at similar measures as other nanomaterials. There has been a lot

of research performed as well as ongoing to mimic the nanoparticle-like virus behavior for designing the target drug release as well as gene delivery regimens (Singh et al. 2017). Therefore, nanotechnology may offer great value in the present ongoing pandemic via various ways such as viral

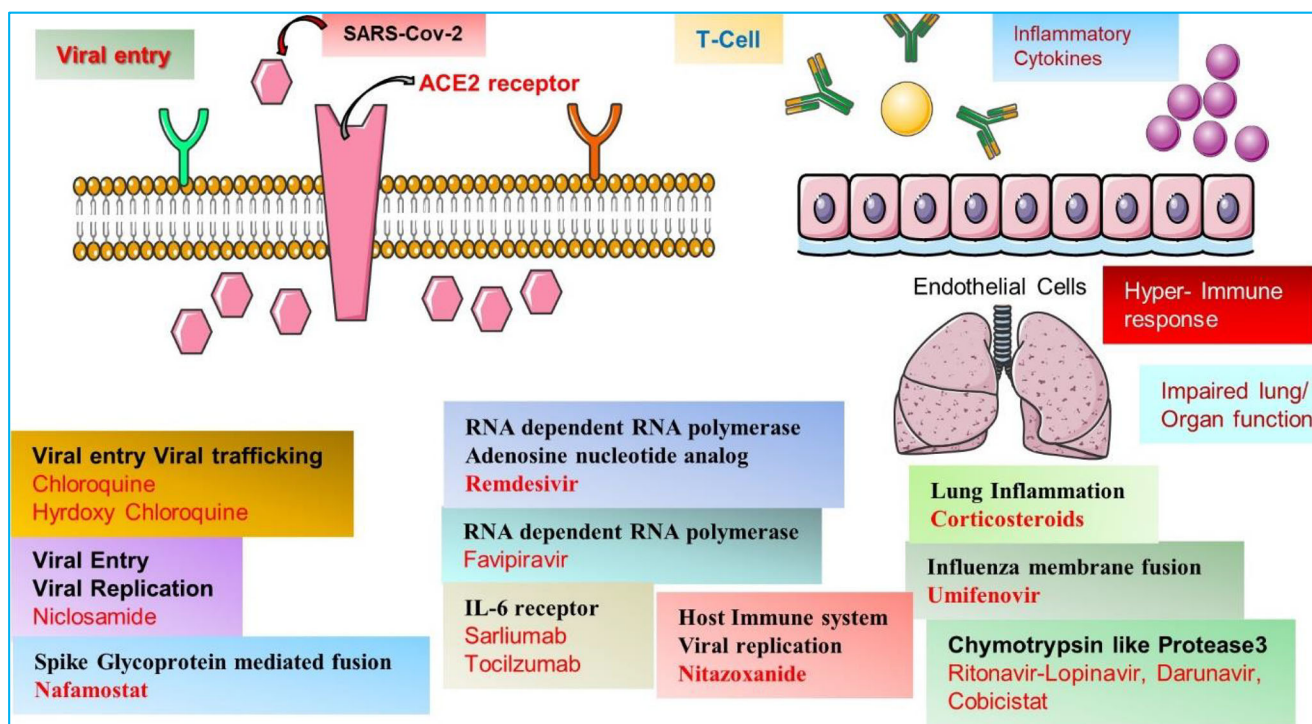


Fig. 5 MOA of drugs for management of SARS COV-2 disease

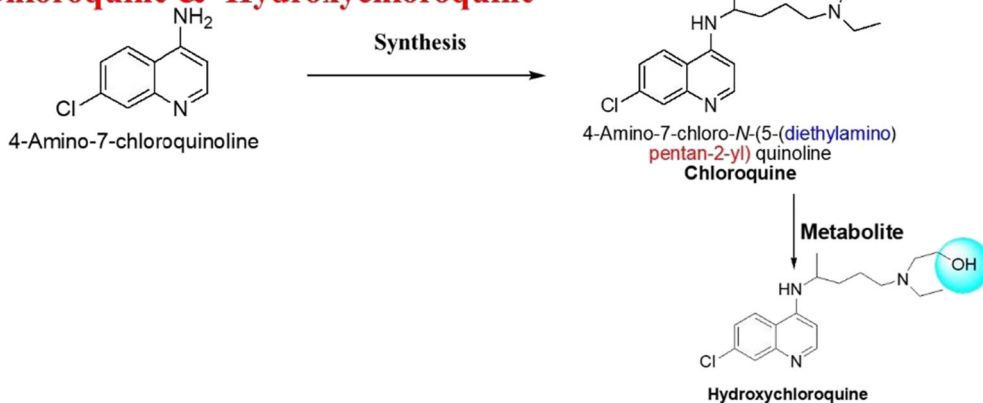
neutralization and detection, vaccine developments, and providing effective treatment (Florindo et al. 2020).

Nanoparticles possess similarity to coronavirus, excluding viral genome if nanoparticles enter the host cells renovate immunity against this type of infection. Due to similar size nanoparticles may bind to the COVID-19 virus and distort its structure along with IR

treatment which further results in hampering the viral survival and reproducibility (Yang 2021).

Various nanoparticles such as gold and carbon quantum dots (CQDs) are excellent options for interacting with the virus as well as averting entry within the cells due to the large surface area as well as a broad range of functional groups. CQDs possess a diameter 10 nm approx. and good water

Chloroquine & Hydroxychloroquine



The effect of hydroxychloroquine and chloroquine on viral replication goes beyond cytokine inhibition. These medications are weak bases that can affect acid vesicles and inhibit several enzymes. This characteristic allows them to inhibit the viral entry to the cell when the endocytosis is pH dependent. It also inhibits glycosyl-transferases, viral post-translational modifications and replication of some viral families.

Fig. 6 Mechanism of chloroquine/hydroxychloroquine

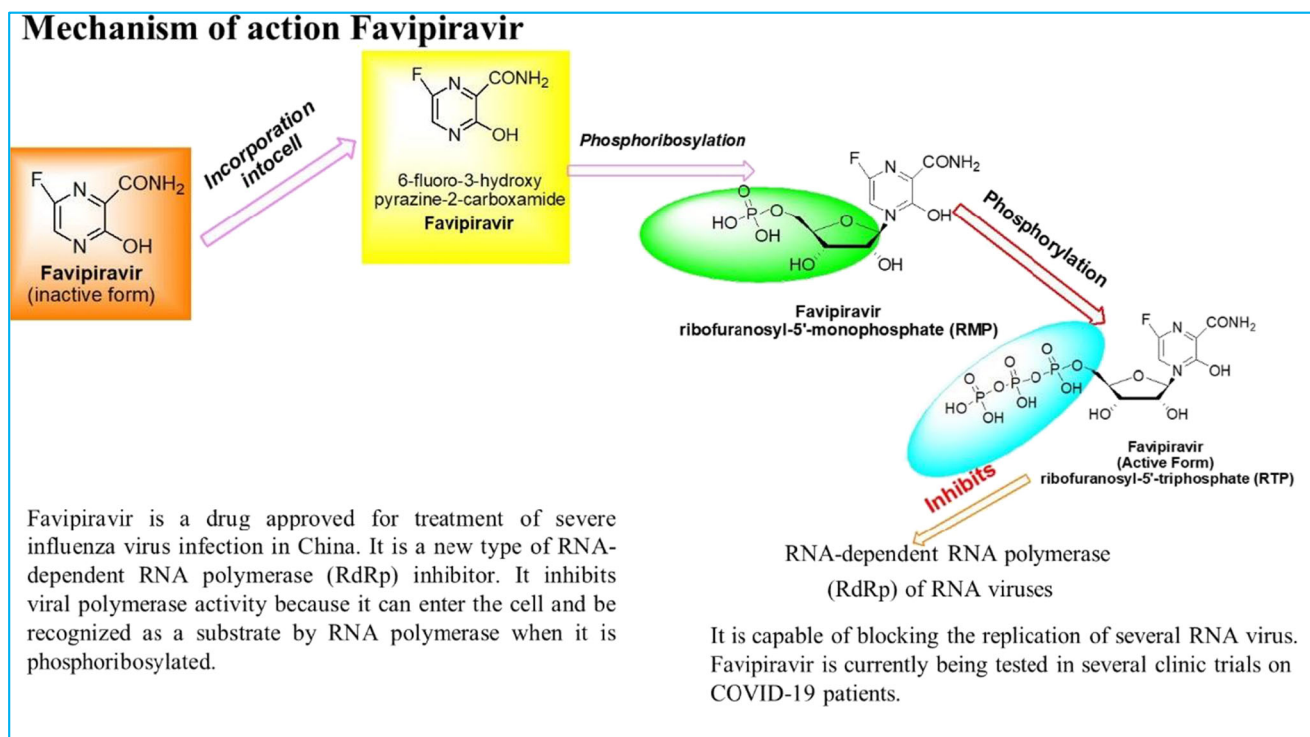


Fig. 7 Mechanism of Favipiravir in the treatment of SARS COV-2

solubility, making it an ideal applicant for conquering coronavirus, due to easy entry through endocytosis and preventing mRNA replication (Wang et al. 2019; Iannazzo et al. 2018).

Gold nanoparticles using extracts impart additional advantages such as being eco-friendly, non-toxic, cost-effective, and easily accessible. Research performed so far revealed that gold

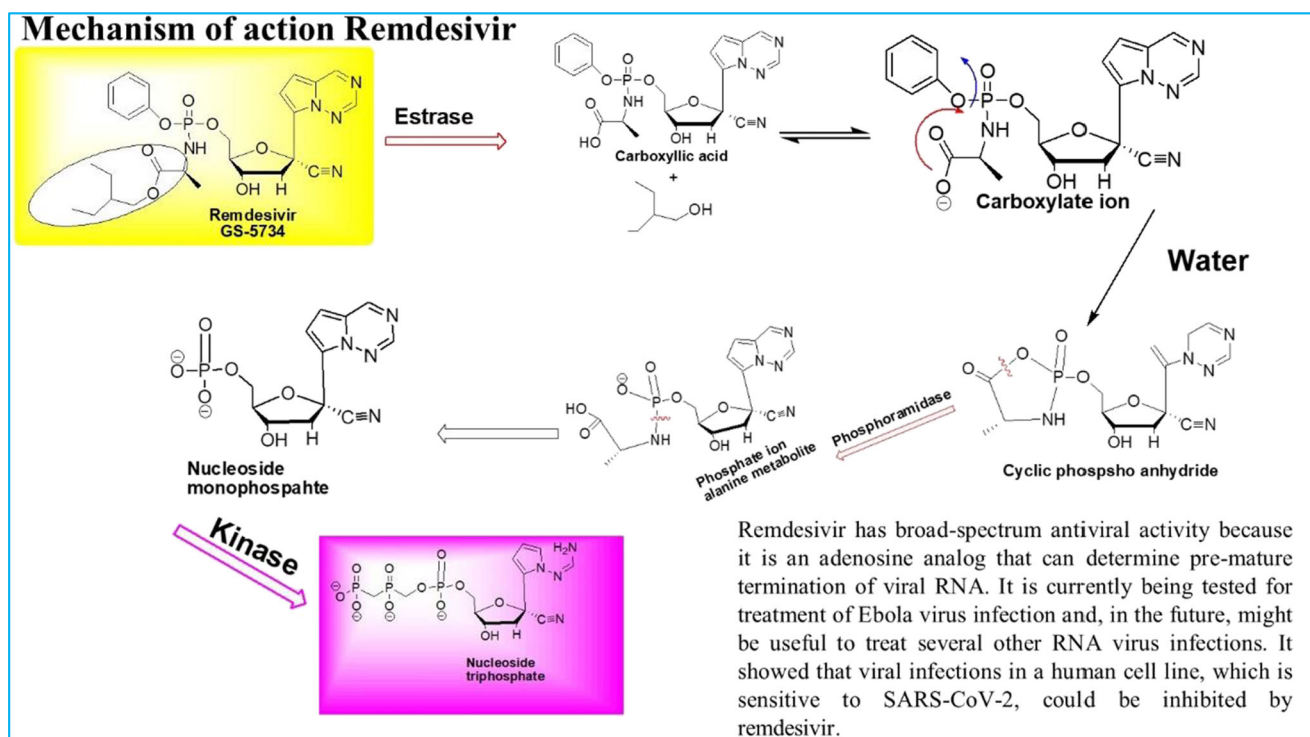


Fig. 8 Mechanism of action of remdesivir in the treatment of SARS COV-2

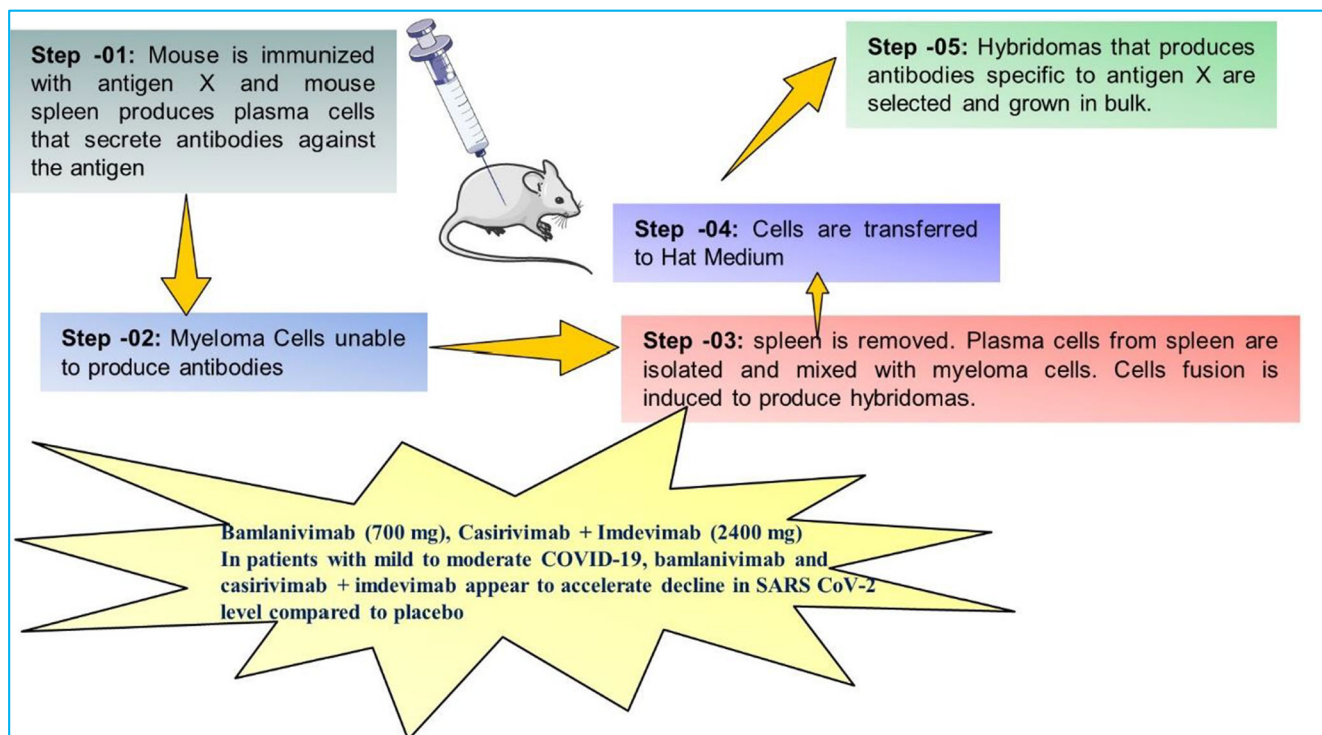


Fig. 9 Production of monoclonal antibodies.

nanoparticles can be stabilized with few polymers (bio-compatible) that might act as antiviral agents against HIV 1, FMDB, diarrhea, dengue, H1N1, H3N2, and H5N1 virus (Medhi et al. 2020). Silver, iron, mesoporous silica (Wang et al. 2017; Lara et al. 2010; Rojas et al. 2020; Rai et al. 2016) and organic particles such as Carbon nanotubes & Nanoparticles Graphene, Polymeric, Lipid-based, Dendrimers revolution in nanotechnology employing novel nanocarriers and magnetic nanoparticles (Comparetti et al 2018; Alidori et al. 2016; Mangum et al. 2006; Singh et al. 2019; Hennig et al. 2015; Figueroa et al. 2019; Pollock et al. 2010; Jain et al. 2011; Shah et al. 2017; Lembo et al. 2018; Li et al. 2005; Clayton et al. 2009; Itani et al. 2020; Williams & Corr 2013) have been documented in the treatment of Covid-19. The current strategies of nanoparticles used in the treatment of COVID-19 infection are shown in Table 7.

Discussion

An epidemic of pneumonia that started in December 2019 (Wuhan-China) has been well known to be due to novel coronavirus, which has been named later as COVID-19. The virus is extremely contagious and results in pandemic situations due to the lack of any medicine for prophylaxis as well as treatment.

Subsequently, searching the effective prophylactic and therapeutic strategies for the management of the disease is still

continuing. Furthermore, the emergency requirement of drugs leads to the repurposing of drugs which has been mentioned in this article. We illustrated categorized response based on infection and contiguity stages of diseases among the human population. Despite the fact that until now no medicine system provides clinically proven treatment for COVID-19, continuous research is ongoing searching for the effective treatment for COVID-19 (Fig. 10) (Silva et al. 2020; Sadlon et al. 2010; Rosa et al. 2020; Jin et al. 2020).

Moreover, vaccines, anti-viral drugs, and antibiotics possess the gold standard for the current preventive measures for different epidemic disorders until now. Furthermore, problems related to developing dispensing, side effects, storage conditions, mutations, and antibiotic-resistant microbes should also be taken into considerations. Novel approaches for communicable diseases are absolutely required and the WHO also mentioned that at the time of the Ebola outbreak in 2014. The expert committee stated that it's unethical to suggest unproven intercession with unknown efficiency as well as adverse effects as promising treatment/prophylaxis. It should be taken into consideration that it's not only COVID-19, but there are also other viruses as well as diseases for their vaccines, and clinically proven treatment is not available. Therefore, innovative research, as well as technique, is absolutely required for providing effective medication to society (Fig. 11) (Veronese et al. 2020; Reyes et al. 2020; Michael and Thompson 2020; Cox et al. 2021; Furuta et al. 2017; Cristian et al. 2020; Chaccour et al. 2021).

Table 5 List of approved vaccines for COVID-19

S. No.	Vaccine	Vaccine type	Developers/country	Status of vaccine	Ref.
1)	RBD-Dimer	Protein subunit	Anhui Zhifei Longcom /China/ Uzbekistan	Approved in 2 countries 6 trials in 5 countries	Shahab et al. (2021); Yan et al. (2021); WHO (2021)
2)	mRNA-1273	RNA	Moderna/USA	Approved in 53 countries 21 trials in 4 countries	Shahab et al. (2021); Yan et al. (2021); WHO (2021)
3)	BNT162b2	RNA	Pfizer/BioNTech Tozinameran, Comirnaty	Approved in 89 countries 26 trials in 15 countries	Shahab et al. (2021); Yan et al. (2021); WHO (2021)
4)	QazVac	Inactivated	Kazakhstan RIBSP/Kazakhstan	Approved in 1 country 3 trials in 1 country	Shahab et al. (2021); Yan et al. (2021); WHO (2021)
5)	Sputnik V	Viral vector (NR)	Gamaleya/ Russian Federation	Approved in 68 countries 19 trials in 6 countries	Shahab et al. (2021); Yan et al. (2021); WHO (2021)
6)	Ad26.COV2.SJNJ-78436735	Viral vector (NR)	Janssen (Johnson & Johnson)/America	Approved in 52 countries 11 trials in 17 countries	Shahab et al. (2021); Yan et al. (2021); WHO (2021)
7)	COVID-19 Inactivated Vaccine	Inactivated	Shifa Pharmed Industrial Co/Iran	Approved in 1 country 4 trials in 1 country	Shahab et al. (2021); Yan et al. (2021); WHO (2021)
8)	AZD1222	Viral vector (NR)	Oxford/AstraZeneca US	Approved in 115 countries 32 trials in 19 countries	Shahab et al. (2021); Yan et al. (2021); WHO (2021)
9)	Covishield(ChAdOx1-nCoV-19)	Viral vector (NR)	Serum Institute/India	Approved in 43 countries 2 trials in 1 country	Shahab et al. (2021); Yan et al. (2021); WHO (2021)
10)	SARS-CoV-2 Vaccine	Inactivated	Minhai Biotechnology Co./China	Approved in 1 country 3 trials in 1 country	Shahab et al. (2021); Yan et al. (2021); WHO (2021)
11)	Covaxin	Inactivated	Bharat Biotech/India	Approved in 9 countries 5 trials in 1 country	Shahab et al. (2021); Yan et al. (2021); WHO (2021)
12)	Ad5-nCoV	Viral Vector	CanSino/China	Approved in 8 countries 8 trials in 6 countries	Shahab et al. (2021); Yan et al. (2021); WHO (2021)
13)	KoviVac	Inactivated	ChumakovCenter/Russian Federation	Approved in 1 country 2 trials in 1 country	Shahab et al. (2021); Yan et al. (2021); WHO (2021)
14)	EpiVacCorona	Protein Subunit	FBRI/Russian Federation	Approved in 2 countries 3 trials in 1 country	Shahab et al. (2021); Yan et al. (2021); WHO (2021)
15)	BBIBP-CorV	Inactivated	Sinopharm/Beijing, China	Approved in 53 countries 7 trials in 7 countries	Shahab et al. (2021); Yan et al. (2021); WHO (2021)
16)	Inactivated (Vero Cells)	Inactivated	Sinopharm (Wuhan)/ China	Approved in 1 country 8 trials in 7 countries	Shahab et al. (2021); Yan et al. (2021); WHO (2021)
17)	CoronaVac	Inactivated	Sinovac/China	Approved in 32 countries 15 trials in 7 countries	Shahab et al. (2021); Yan et al. (2021); WHO (2021)
18)	TAK-919	RNA	Takeda	Approved in 1 country 2 trials in 1 country	Shahab et al. (2021); Yan et al. (2021); WHO (2021)

* Center for Genetic Engineering and Biotechnology, ** Instituto Finlay dVacunas; NR non-replicating

Table 6 List of vaccines in phase 3 clinical trial

S. No.	Vaccine	Vaccine type	Developers/country	Status of vaccine	Ref.
1.	Recombinant (Sf9 cell)	Protein Subunit	West China Hospital/ China	5 trials in 1 country	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021)
2.	COVOVAX	Protein Subunit	Serum Institute of India/ India	2 trials in 1 country	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021)
3.	CIGB-66	Protein Subunit	Center for Genetic Engineering and Biotechnology (CIGB)/	5 trials in 1 country	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021);
4.	Recombinant Protein	Protein Subunit	Sanofi/GSK/USA	5 trials in 2 countries	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021)
5.	SCB-2019	Protein Subunit	Clover Biopharmaceuticals AUS Pty Ltd/Australia	5 trials in 10 countries	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021)
6.	UB-612	Protein Subunit	Vaxxinity, Inc./Taiwan	4 trials in 1 country	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021)
7.	NVX-CoV2373	Protein Subunit	Novavax/USA	8 trials in 7 countries	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021)
8.	EpiVacCorona	Protein Subunit	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology “Vector” (FBRI)/Russian Federation	Approved in 2 countries 3 trials in 1 country	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021)
9.	Nanocovax	Protein Subunit	Nanogen Pharmaceutical Biotechnology Joint Stock Company (Nanogen)/ Viet Nam	3 trials in 1 country	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021)
10.	FINLAY-FR-1A	Protein Subunit	Instituto Finlay de Vacunas Cuba/ Cuba	3 trials in 1 country	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021)
11.	FINLAY-FR-2	Protein Subunit	Instituto Finlay de Vacunas Cuba/ Cuba	3 trials in 1 country	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021)
12.	Plant-based- VLP	VLP	Medicago/ Canada	3 trials in 2 countries	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021)
13.	AG0302-COVID19	DNA	AnGes/ Japan	4 trials in 1 country	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021)
14.	ZyCoV-D	DNA	Zydus Cadila/ India	5 trials in 1 country	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021)
15.	INO-4800	DNA	Inovio/USA	6 trials in 3 countries	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021)
16.	CVnCoV	RNA	Curevac/ Belgium, Germany	11 trials in 12 countries	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021)
17.	BNT162b1	RNA	Pfizer/BioNTech/ Germany	5 trials in 3 countries	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021)
18.	mRNA	RNA	Walvax/ China	4 trials in 1 country	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021)
19.	GRAd-COV2	Non Replicating Viral Vector	ReiThera/ Italy	5 trials in 12 countries	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021)
20.	VLA2001	Inactivated	Valneva/ United Kingdom of Great Britain	4 trials in 1 country	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021)
21.	Inactivated (Vero Cells)	Inactivated	Chinese Academy of Medical Sciences/ China	5 trials in 3 countries	Regulatory Focus (2021); Covid-19 Vaccine tracker (2021)

Challenges and issues observed during vaccine development

Vaccine development takes an average of 10–15 years, and compressing it to just 15 months has its own set of drawbacks and issues. Combining stages to accelerate vaccine

development necessitates testing on smaller groups. This is a major issue because, if the vaccine is made available to the general public, unexpected adverse effects may develop in bigger groups that were previously undetected in smaller groups. Furthermore, if all individuals with comorbidities are not properly addressed in the design of clinical trials,

Table 7 Current strategies on nanoparticles

S. No.	Nanoparticles	Attributes	Mechanism of action	Current status	Ref.
Inorganic particles					
a.	Gold AuNPs	A strong bond in Au and thiol ligands. Recently research revealed about AuNPs-sulfonate mercapto ethane sulfonate (MES) along with MUS undecanesulfonic acid may cause irreversible distortion against viruses including respiratory syncytial virus, in both in-vitro, in vivo analysis.	AuNPs-MES-MUS complex Showed multivalent binding on to virus surface results in collapsing of the viral capsid. The multivalent binding mechanism might play a significant role against COVID-19 battle.	It has been shown that when AuNP’s functionalized with sugars like glucose or lactose-based ligand may play a significant role in the treatment of Dengue. Length and surface area of the molecule may affect the inhibitory activity up to a greater extent.	Wang et al. (2017)
b.	Silver AgNPs	AgNPs may possess antiviral potential can be used without surface modifications.	Mechanism of action of antiviral potential may be of three probable mechanisms- AgNPs may react to glycoproteins at virus surface Block RNA replication, Interfere with cell attachment at the cell surface, and avoiding virus fusion. AgNPs (naked) possess restrictions due to the inherent cytotoxicity it exhibits.	Curcumin-loaded AgNPs revealed high antiviral potency against Respiratory Syncytial Virus (RSV) showed no cytotoxicity even after incubation of cells. Morris et.al, established PVP-AgNPs of size 10nm against RSV at a concentration that exhibited a strong antiviral potential with nil cytotoxicity against epithelial cells.	Lara et al. (2010)
c.	Iron oxide IONPs	IONPs are widely used as contrast agents in MRI, biocompatible and magnetic characters enabling IONPs as superparamagnetic under the influence of the external magnetic fields.	NPs have been observed to possess significant virucidal potential via amino alkylation of genome lads to arresting replication and viral inactivation.	Mannose-loaded IONPs for dendritic delivery have been shown a significant increase in IL-6, TNF- α , and IFN- γ has been observed in dendritic cells in in-vitro analysis. Recent research showed that interaction between SARS-CoV-2 and hemoglobin results in denaturation of hemoglobin and thus dysregulates the iron mechanism which may lead to other complications.	Rojas et al. (2020)
d.	Mesoporous silica MSNPs	Another nano-approach of mesoporous silica possesses integrate pore size, can accommodate molecules for codelivery.	This character makes these an excellent platform for inactivating the entry as well as averting the viral replication of COVID-19 within the host cell.	MSNPs-lipid and (E)-2-(1,4-dimethylpiperazin-2-ylidene)amino)-5-nitro-N-phenyl benzamide (ML336) complex have been established in order to enhance the antiviral circulation period and its biocompatibility. In vitro results showed dose-dependent viral inhibition whereas in vivo results revealed significant antiviral potential with no toxicity.	Rai et al. (2016)
Organic particles					
1.	Carbon nanotubes and NP’s graphene, e.g., carbon nanotubes (CNTs), Graphenes, fullerenes NP’s	CNTs possess sp ² +sp ³ hybridization with outstanding electric conductivity makes them perfect for research fields. SWCNT and MWCNT folded with graphene sheets of diameter 5-20nm and length (50-1,000nm) can be used for research. Toxicity limits the use of CNT’s in COVID-19	Hussain et al reported that when CNT’s associated with biomolecules may reduce the inflammation significantly as well as cytotoxicity to the respiratory system.	This technology might be exciting for providing possible treatments to COVID-19 patients. Because of NPs. However, immune cell activation and inflammation through carbon NPs can be reduced but presently it is not recommended in therapy.	Comparetti et al. (2018); Alidori et al. (2016); Mangum et al. (2006)

Table 7 (continued)

S. No.	Nanoparticles	Attributes	Mechanism of action	Current status	Ref.
3.	Polymeric NP's	<p>management. These limitations can be overcome by the functionalization of CNT's.</p> <p>These NPs can be engineered for target-specific delivery of drug may inhibit virus attachment to cell through the receptor. Which can ultimately help in the reduction of disease and adverse effects, enhancing safety as well as overcoming drug resistance.</p>	<p>These can block the interaction of SARS-CoV-2 with ACE2 receptors may assist in controlling the viral infection. Polymers such as PEG and poly-amidoamine may bind its ACE2 receptors and act as antagonists with a virus.</p> <p>Angiotensin loaded combined with angiotensin enzyme may be the best opportunity for future drug delivery studies.</p>	<p>Methodretaxate-loaded NPs have been authorized in Brazil are in phase I & II clinical trials (NCT04352465). This study revealed the effectiveness as well as safety above NPs in severe inflammation in lung injury throughout the management of COVID-19 patients. Multi-functional nanocarriers with polymers have been authorized at novel nanoplatfroms for therapeutic application which could be instantly employed for safe usage in this pandemic situation.</p> <p>(U.S. National Library of Medicine 2020).</p>	<p>Singh et al. (2019); Hennig et al. (2015); Figueroa et al. (2019)</p>
4.	Lipid-based NP's	<p>Enormous potential, biodegrade easily, good biocompatibility, and available in various forms such as LCNPs, NCLs, microemulsions, nanoemulsions, SLNs, etc.</p>	<p>LbNPs have been employed for the treatment of various diseases such as HIV, HCV, herpes, HBV, and hepatitis B (HBV).</p> <p>Research showed that the use of PEG in liposomes enhances macrophage intake irrespective of corona formation. This is an interesting approach for searching the treatment against COVID-19.</p> <p>These targeted liposomes can speed up the cellular uptake may also slow down the virus response in infected cells can impart recovery of infected cells.</p>	<p>Marketed formulations Doxil, AmBisome</p>	<p>Pollock et al. (2010); Jain et al. (2011); Shah et al. (2017); Lembo et al. (2018)</p>
5.	Dendrimers Revolution in nanotechnology employing novel nanocarriers	<p>Enhance the efficiency of phytoconstituents and drugs. Exceptional physiochemical properties like less polydispersity, solubility, efficient drug encapsulation capability, biodegradability, and compatibility make dendrimers valuable agents for hydrophobic drugs.</p>	<p>Unique physicochemical properties, such as solubility, low polydispersity, effective drug encapsulation</p> <p>Dendrimers can form strong viral interactions enhance antiviral activity, establish them as potential systems against.</p>	<p>A commercially accessible dendrimer is SPL7013 Gel (VivaGelR), which is a microbicide that contains bivalent benzhydryl amine (BHA) center with 4 lysine branches formulated for the inhibition of HIV and HSV infections.</p>	<p>Li et al (2005); Clayton et al. (2009); Itani et al. (2020)</p>
6.		<p>Iron oxide NPs</p>	<p>The cDNA of the virus can be amplified via PCR &</p>	<p>Recently, MNPs have been employed for COVID-19 detection.</p>	

Table 7 (continued)

S. No.	Nanoparticles	Attributes	Mechanism of action	Current status	Ref.
	Magnetic nanoparticles (MNPs)	Silica coated supramagnetic NPs	isolation through the use of a magnetic field. Augmented cDNA can be distinguished by hybridization or silica-coated NP (SFNP) with fluorescent technique. The detection limit 2.0×10^3 samples within 6 h.	Research reported the use of iron oxide coated with silica for RNA extraction from the sample.	Williams and Corr (2013).
7.	Quantum dots Detection of viruses	Unique optical and electrical properties	QD-linked RNA particularly against SARS-CoV N protein has been informed to possess high sensitivity for detection of restrained viral protein on intended chips.	Marketed QD-605 possess emission maxima (605nm) to access an excellent detection limit of 0.1 pg/mL against SARS-CoV N through confocal laser scanning microscopy.	Iannazzo D et al. (2018)

unexpected adverse effects may be discovered in those groups once the vaccine is ready for general use. Vaccines would be examined for similar adverse effects in the broader population under post-marketing surveillance. It’s uncertain how mRNA vaccines will be developed since in past researches. Nucleic acid–based vaccines like DNA and RNA have failed to generate viable vaccinations for human diseases in the past. Because lipid nanoparticles are temperature sensitive, scaling up production may be difficult. Pre-existing adenovirus immunity is a concern, particularly for vaccine candidates that utilize human adenoviruses, such as CanSino’s Ad5 vaccine, since it may reduce the vaccine’s immunological response (Sharma et al. 2020).

In order to meet pandemic demand, rapid large-scale vaccine production remains a challenge fraught with uncertainties. Because phase 3 trials need more than 30,000 individuals and are performed later in the study phase, there is a high chance that there will be fewer instances of COVID-19 at that time, requiring HCTs. Despite the fact that HCTs have been utilized in the past, they may pose a higher risk for COVID-19 due to a lack of understanding of the disease's genesis and the absence of a feasible treatment. As an alternative to HCTs, several vaccine candidates have taken advantage of transmission rate differences by starting phase 3 trials in countries with a higher SARS-CoV-2 infection rate to

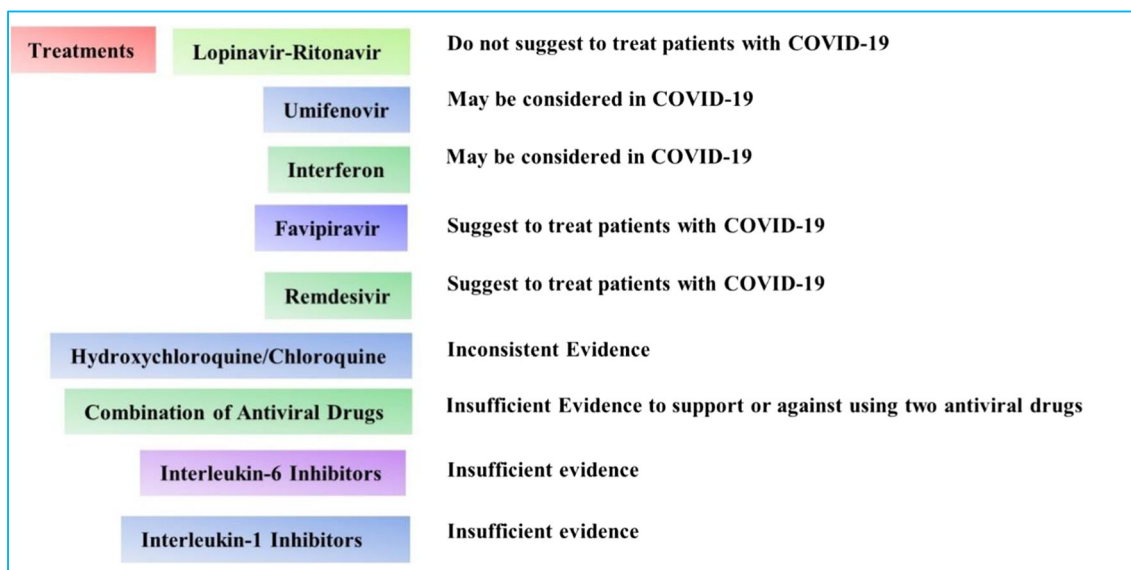


Fig. 10 Drugs and their effectiveness in the treatment of mild to moderate infection

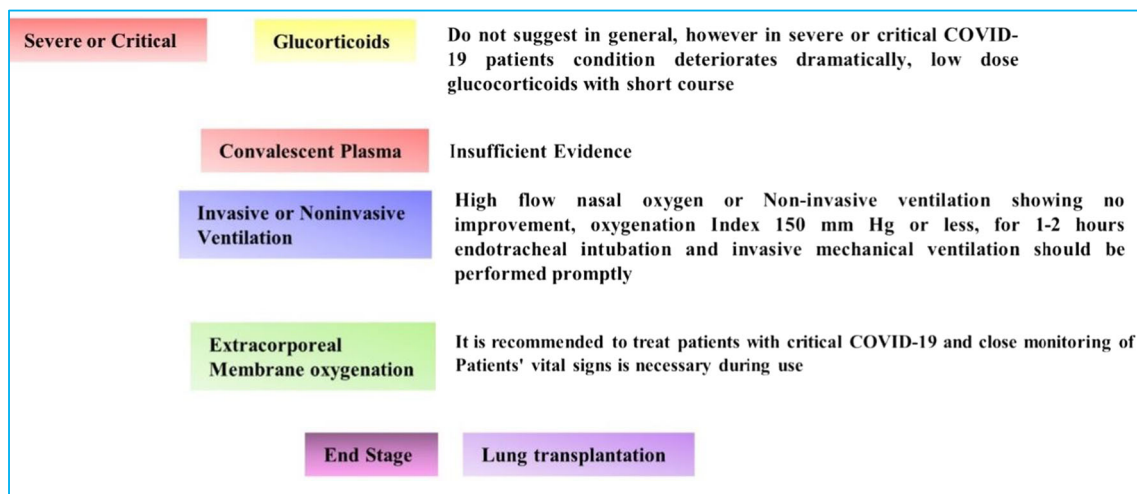


Fig. 11 Drugs and their effectiveness in severe infection of SARS COV-2

ensure that a significant number of patients can participate. Vaccines against the virus may be ineffective due to the virus's mutations. However, given the urgent need for a COVID-19 vaccine to be accessible globally, being concerned about and analyzing such risks should not prevent the public introduction of otherwise safe and effective vaccines (Sharpe et al. 2020, Morris 2020, Sharma et al. 2020).

Future perspective

The COVID-19 pandemic is still a global health issue that has impacted a vast number of people. From December 2019 onwards, most nations around the world have recorded a substantial number of COVID-19 cases. There are currently no effective vaccinations or medications available to prevent COVID-19 infection. To address these health issues, various research groups are working to determine the most effective treatment for COVID-19 by delivering FDA-approved antiviral medicines such as oseltamivir, ritonavir, remdesivir, ribavirin, and favipiravir, among others. Simultaneously, scientists are concentrating on the creation of several types of vaccinations that can prevent COVID-19 infection. According to the survey results, research will continue until acceptable drug candidates and vaccines are found based on pathological conditions, physiology, clinical symptoms, diagnosis, and public health emergencies.

Conclusion

Keeping in view of this epidemic, we're still waiting for precise COVID-19 treatment and care. Although a few medicines, such as remdesivir, ribavirin, and favipiravir, are prescribed for the therapy, it is difficult to employ them specifically for the treatment of COVID-19 infection due to a lack of

clinical data. These medicines were discovered to have a high affinity for the COVID-19 primary protease. Antimalarial medications like chloroquine and hydroxychloroquine, on the other hand, had a strong binding affinity with the SARS spike glycoprotein and the ACE2 complex. Vaccination has begun in India, although clinical data on safety and efficacy will not be available for some time. Even after immunization, everyone should be upbeat and follow the instructions to the letter. It's also been noted that we're dealing with not only COVID-19 but also its fear, particularly in India.

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