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Review article

Current Potential Treatment Strategies for the Deadly, COVID-19

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Abstract

Coronavirus disease (COVID 19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the latest threat to the global health which has devastated human life, health and economy to extreme condition. Due to this, the entire world has faced lockdown for the first time in decade. Till now, no drugs have been approved for treatment of COVID 19, it is managed by timely diagnosis and treatment based on symptoms. The outbreak of the disease has been so rapid that the entire world is under fear. The report of this pandemic situation given by WHO is alarming the need for developing effective medication to combat the devastating scenario. So, we have conducted extensive review on different drugs, their mechanism, various vaccines which are undergoing clinical trial and those who have got some satisfactory outcome. Apart from this, plasma therapy has also shown some promising results against COVID 19, where 200-300 ml plasma infusion is given to COVID 19 patients. Since the need of the hour is to get an effective treatment strategy on an emergency basis, so a vast investigation will reveal the treatment strategy which has got some promising results. This review highlights various drugs, vaccines and plasma, their mechanism of action and dose at which they can be effective against COVID 19 as well as their clinical trial status and report. Thus this review, summarizes all the possible treatment strategies that can be effective against the global pandemic.

Introduction

Every dark cloud has a silver lining. It was until 2002 that corona was considered as a non fatal virus. Then it proved its fatality with rapid widespread of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 [1, 2] and Middle-East respiratory syndrome coronavirus (MERS-CoV) in 2012 [3]. Now in the year 2019, the entire world is facing the serious devastating effects of corona virus disease (COVID 19) on human lives, health system and economy due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4, 5]. It was first reported to World Health Organization (WHO) on December 31, 2019. WHO declared the outbreak of COVID-19 as global health emergency on 30th January 2020 and as global pandemic on 11th March 2020 [6]. It has become a serious pandemic threat worldwide and requires immediate solution. The outbreak of COVID 19 started in China in December 2019 and now it has affected every continent except Antartica. Globally, as of 31st December 2020, there have been 83,068,034 confirmed cases of COVID-19, including 1,812,208 deaths, reported to WHO [7]. Along with this, millions and millions of people's lives are continuously being affected due to mandatory isolation. Thus COVID 19 outbreak has potentially brought major challenges and far reaching consequences on global health system and economy.

Coronavirus are spherical in shape and they contain single-stranded positive sense RNA covered with club shaped glycoprotein that project out from their surface just like a

crown [8]. They have four sub types: alpha, beta, gamma and delta corona virus, out of which, SARS-CoV-2 is beta type corona virus. This betacoronavirus genome encodes several structural protein: spike (S) protein, envelope(E) protein, membrane (M) protein, and nucleocapsid (N) phosphoprotein [9]. Among these, the glycosylated spike (S) protein functions binds to a receptor protein, Angiotensin-converting enzyme 2 (ACE2) which is located on the surface membrane of host cells and thus induces the host immune response. SARS-CoV-2 uses a protease called TMPRSS2 (Transmembrane Serine Protease 2) to enter into the cells and infect them [10-12].

Since no specific antiviral drugs have been approved by FDA for prevention or treatment of COVID-19 till date, the current demand of the situation is to provide a cost-effective, safe, and easily available pharmaceutical dosage form to prevent the rapid global spread of SARS-CoV-2. Herbal medication also have played a significant role in combating infectious diseases and in promoting the belief, that herbal medicine profits from a number of herbal medicine studies for treating SARS Coronavirus (SARS-CoV) and that it has a beneficial impact on the diagnosis and the prevention of viral diseases. The aim of this review is to collect and summarize the information from various recent scientific trials conducted to manage the infection. It highlights the promising new drug molecules and adjunctive agents, their mechanism of action and their comparative analysis. The review also throws light on various drugs undergoing clinical trial and their current status so that we can help the nation and the world by joining hands against the deadly COVID 19.

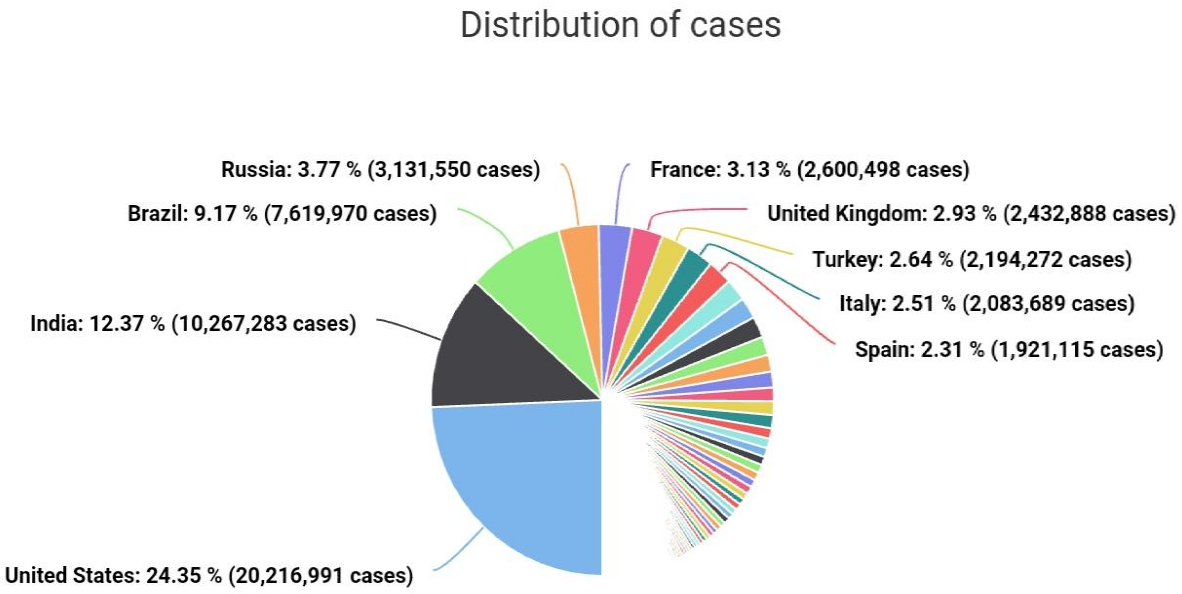


Figure 1. Pie graph representing distribution of Corona virus positive cases in different countries throughout the world (as of 31st Dec, 2020) [6].

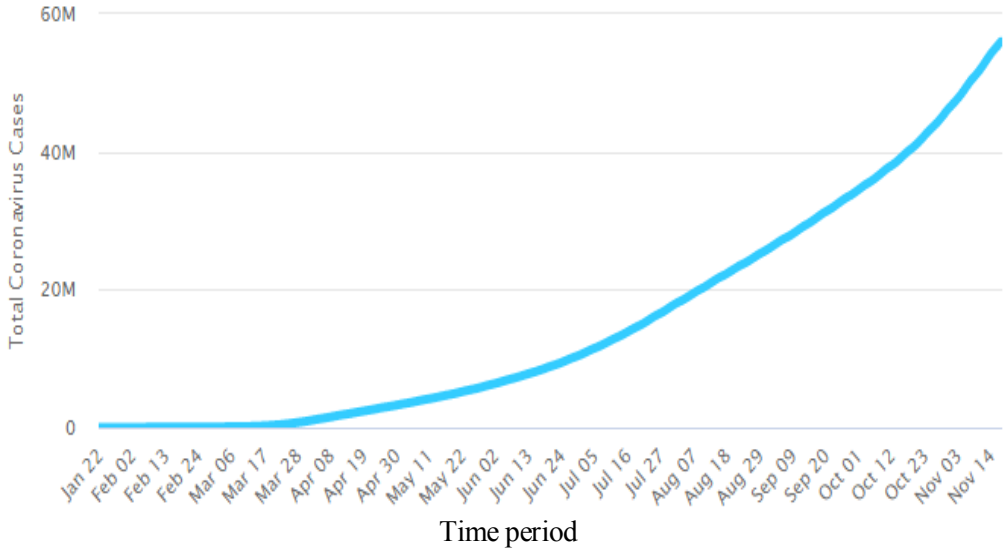


Figure 2. Graph representing the total number of coronavirus cases in world each day in the year 2020 [6].

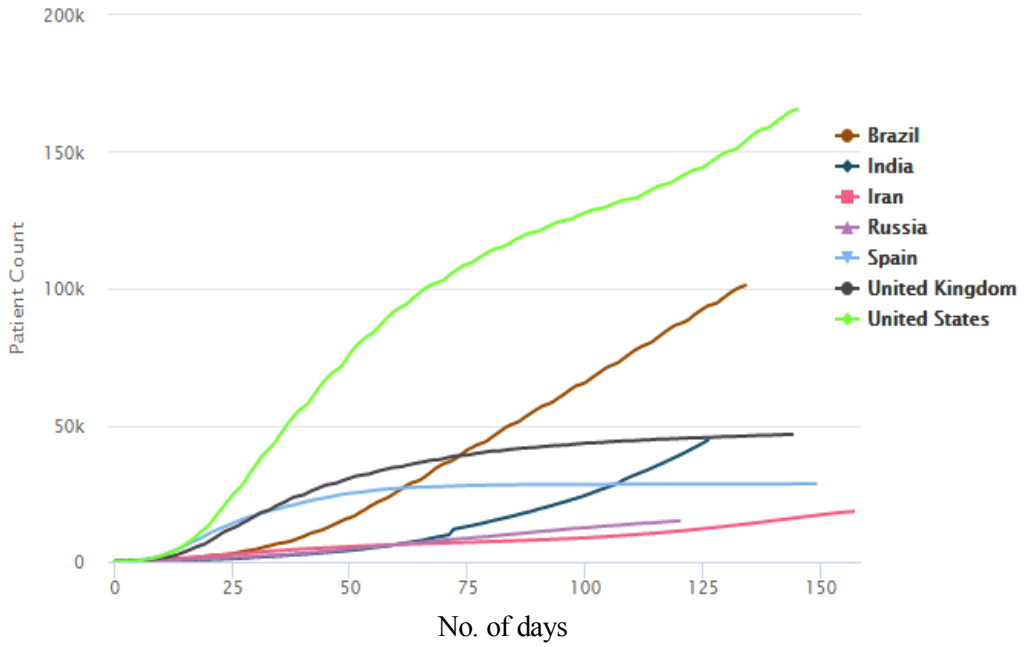


Figure 3. Graph of number of patient Vs number of days representing cumulative number of deaths (by number of days since 100 deaths) [6].

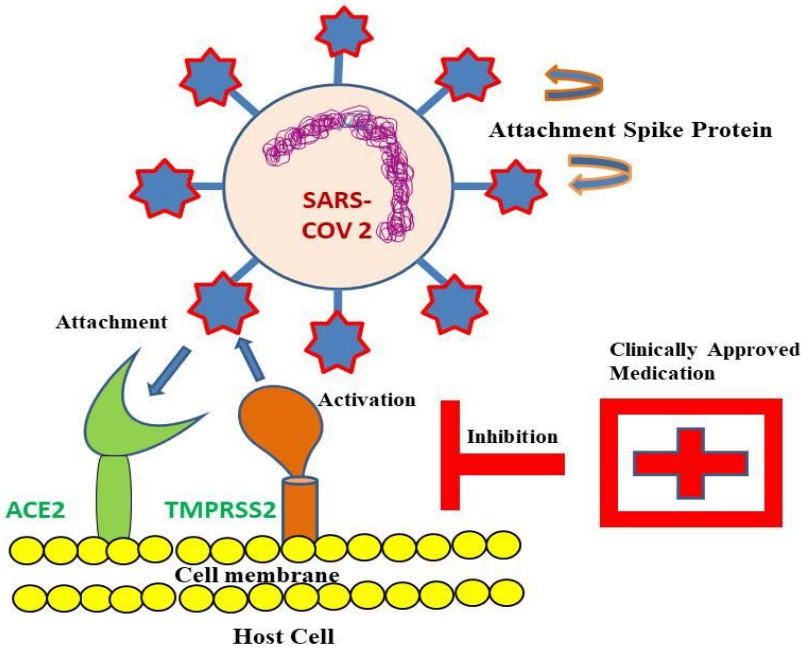


Figure 4. The attachment of spike protein of SARS-CoV2 with ACE2 and its activation by cellular protease TMPRSS2 [12].

Methodology

Extensive literature survey has been done to accumulate the data which can provide information needed for the treatment and prevention of COVID 19. The survey started with the papers published in high impact journals from several sites like Pubmed, Science direct, Web of science. The search was also done along the site of FDA, WHO, Clinical trial. The keywords used for the search includes COVID 19, treatment, prevention, drugs used, case studies, convalescent plasma, vaccines, current update on corona virus, current works in clinical trial and so on. Many research and review papers as well as case studies were the source of information. Current status of the treatment protocols were obtained from the website, clinical trial.gov.in

Transmission

The various routes of transmission for SARS-CoV-2 are through touch, via droplet, blood borne, airborne, oral, mother-to-child as well as animal-to-human transmission [13]. Saliva and respiratory secretions expelled by infected person during coughing, sneezing, talking causes transmission [14-17]. Spread of infectious agent also occurs

by distribution of infectious droplet nuclei which remains suspended in air for prolong period and throughout long distances [18]. Contact with surfaces or objects which has been contaminated with virus from an infected person followed by touching mouth, nose, or eyes also transmits the corona virus. SARS-CoV-2 RNA have been detected in urine as well as in excreta of some patients where viable SARS-CoV-2 was found in the urine of a patient [19-22]. Some studies have detected SARS-CoV-2 RNA in plasma and serum but the virus has found to divide in blood cells at a very low rate. Some studies have shown that in few breast milk samples obtained from infected mothers, viral RNA fragments have been detected but they were not viable so breast feeding is not yet found to transmit the disease [23]. A SARS-CoV-2 infected person can transmit the virus 1-3 days before the onset of symptoms with the highest viral load around the day of onset of symptoms which gradually decreases over time [24-26]. Multiple studies have found that most people infect others before they themselves become ill [27]. The transmission can be prevented by identifying the suspect cases as fast as possible and isolating the infectious person.

Symptoms

COVID-19 affects people in different ways. Most people will develop symptoms within 5-6 days of infection but some may remain asymptomatic. Most common symptoms are fever, dry cough, tiredness. Other symptoms are body aches, sore throat, diarrhoea, conjunctivitis, headache, loss of taste or smell, skin rash and even discolouration of fingers or toes. Person with difficulty in breathing or shortness of breath, chest pain or pressure and loss of speech or movement requires immediate hospitalization [28]. It also causes acute respiratory distress syndrome (ARDS), acute renal injury, acute respiratory injury, septic shock and ventilator-associated pneumonia. In older patient or patients having diabetes, hypertension, cardiovascular disease, cancer are at major risk. In the most severe cases, infection can cause pneumonia, severe acute respiratory syndrome, kidney failure and even death [29].

Pathogenesis

After the virus enters the host cell, the viral RNA genome gets released in the cytoplasm and translates to form two polyproteins and structural proteins, after which the viral genome starts to divide [30]. Glycoprotein formed as the envelope gets itself inserted into the membrane of endoplasmic reticulum and genomic RNA and nucleocapsid protein combines to form nucleocapsid. As a result the viral particles develop to form endoplasmic reticulum-Golgi intermediate compartment (ERGIC). The vesicles loaded with viral particles fuse with plasma membrane releasing the virus [31]. Respiratory system is the major area targeted by COVID 19 infection causing severe pneumonia, RNAaemia, which combines the chance of ground-glass opacities, and acute cardiac injury [30]. High level of cytokines and chemokines were found to be present in the blood sample of COVID 19 infected patients. It was also found that high level of pro-inflammatory cytokines in COVID infected patients increased the severity of disease leading to admission in intensive care unit [32].

Treatment strategies

Lungs have greater number of alveolar epithelium cells expressing ACE2 which allows replication of corona virus in the lungs, making it the most targeted organ for COVID 19. The ACE2 receptor was found to express in kidney, endothelium, pharynx, heart and intestine [33, 34]. So a potential treatment targeting lungs can prevent the infection and its spread to other tissues. The spike protein, S on the surface of SARS-Cov-2 bind with ACE2 binding receptor in presence of TMPRSS2 for entering into the host cell and thus cause infection [35]. So a medicament which can prevent virus entry into the host cells by either inhibiting the protease or by inhibiting the binding of ACE2 with the virus will be effective against COVID 19.

Currently used drug under study for treatment of COVID 19

Remdesivir: Remdesiver has gained emergency use authorization for treatment against COVID-19 by US FDA. Remdesivir (also called GS-5734) is a monophosphoramidate prodrug of an adenosine analogue that has a broad antiviral spectrum coronaviruses [36, 37]. In vitro, remdesivir inhibits all human and animal corona viruses including SARS-CoV-2[37, 38]. Remdesivir acts by inhibiting SARS-CoV-2 replication in human nasal and bronchial airway epithelial cells [39].

Favipiravir: Marketed under the brand Avigan, the drug works by preventing the virus from replicating in cells. Favipiravir triphosphate is a purine nucleoside analogue, which acts as a competitive inhibitor of RNA-dependent RNA polymerase [40]. It has activity against influenza A and B, several agents of viral haemorrhagic fever and SARS-CoV-2 *in vitro* [41].

There are some drugs which affect viral host entry and interferes with viral replication and can be used against COVID 19 are listed in Table no. 1[42].

Table 1. List of drugs and their mechanism of action against covid 19 [42].

Sr. No.	Mechanism	Drug
Affects viral host cell entry		
1	An S protein based antiviral	Vaccine development based on a) S1 subunit of SARS-CoV-2 b) SARS-CoV-2 S protein antiviral
2	Inhibition of (serine protease) TMPRSS2 activity	Camostat mesilate Nafamostat mesilate Bromhexine Antiadrogen
3	Affects viral fusion and uptake	Chloroquine Hydroxychloroquine Hydroxychloroquine sulfate
4	Blocking or changing of the ACE2 receptor	Chloroquine Hydroxychloroquine
5	Delivery of soluble ACE2	Recombinant human ACE2
6	Inhibition of cathepsin B/L	E-64d, an epoxysuccinyl cathepsin inhibitor Miraziridine Tokaramide Quercetin
Interference with viral replication		
7	Interference with RNA-dependent RNA polymerase	Remdesivir (GS-5734)
8	Inhibition of (cysteine proteases) 3CLpro and PLpro activity	lopinavir/ritonavir Quercetin Bromhexine Chloroquine
9	Removes viruses by enabling immune cells to engulf them and reduces the gathering of inflammatory cells and prevents tissue damage produced by the sudden activity inflammatory cells.	EC-18 (derived from Sika deer antler) (Enzychem submits IND for trial of Covid-19 treatment)

Current researches on clinical trials done on COVID-19

1. An investigational monoclonal antibody, **LY3819253 (LY-CoV555)** was made by Eli Lilly and Company and discovered by AbCellera. LY-CoV555 is IgG1 monoclonal antibody (mAb), potent towards SARS-CoV-2 spike protein. It blocks the attachment of virus preventing entry into human cells. The virus gets neutralized potentially which prevents and treats COVID-19. This antibody was isolated from the blood sample of a recovered COVID-19 patient. Since this antibody is generated by immune system of a recovered patient, studies have found it to be effective against corona virus. It is injected into the vein of patients and samples are collected from the back of the nose at different time during the study to estimate the presence of virus in the body. A Randomized, Double-blind, Placebo-Controlled, Phase 2 is carried out in 400 patients from 17th June 2020 to 5th November to study its efficacy and safety in Participants with mild to moderate COVID-19 illness [43].

It has successful completed Phase 1 clinical trial with 40 patients from 28th May 2020 to 23rd August 2020 [44].

2. An investigational **mRNA-1273** vaccine has been developed to prevent COVID-19, manufactured by modernaTX, Inc., and NIAID. mRNA-1273 is a novel lipid nanoparticle (LNP)-encapsulated nucleoside modified messenger RNA (mRNA) -based vaccine that encodes for a full-length, prefusion stabilized spike (S) protein of SARS-CoV-2. A Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study is carried out to check the efficiency, safety, and immunogenicity of mRNA-1273 for preventing COVID-19 up to 2 years of taking second dose of mRNA-1273. In this study, patient is given 1 intramuscular (IM) injection of 100 microgram (ug) mRNA-1273 on Day 1 and on Day 29. The study is being carried out in 30000 participants from 27th July 2020 to 27th October 2020 [45].

3. Duvelisib (Copiktra), an anticancer drug, is currently being explored as treatment to reduce lung inflammation in hospitalized patients with coronavirus disease 2019 The investigators hypothesize that PI3K inhibition with Duvelisib could potentiate hyper activation of the innate immune system, polarizing macrophages, reducing pulmonary inflammation, and thereby limiting viral persistence, improving patient outcomes. A Pilot Study of Duvelisib to combat COVID 19 with 28 participants is designed to commence on 30th September 2020 [46].

4. Decitabine can be used for Coronavirus (COVID-19) Pneumonia- Acute Respiratory Distress Syndrome (ARDS) Treatment. This nucleoside metabolic inhibitor also treats myelodysplastic syndromes (MDS). A randomized double blind placebo controlled Phase 2 trial with a 12 patient lead-in to evaluate safety, prior to full enrollment to an additional 28 patients (for a total of 40 patients) is carried out to assess efficacy of decitabine for treating critically ill patients with COVID-ARDS on 29th July, 2020 [47].

5. Infliximab and Infliximab-abda are TNFα inhibitors currently FDA-approved for the treatment of autoimmune disorders, including Crohn's disease and rheumatoid arthritis. Janssen Biotech markets this chimeric monoclonal antibody. Infliximab fights against tumor necrosis factor alpha (TNF-α). The investigator have put the hypothesis that it will prevent further clinical deterioration and reduce the need for advanced cardio respiratory support and thus prevent early mortality. A Phase 2 Trial of Infliximab in Coronavirus Disease 2019 have been started in June 2020 with 17 participants [48].

6. Tramadol due to its anti-inflammatory, hypocoagulatory, antioxidant, antitussive, bactericidal, cardio-protective, analgesic and antidepressant property, can be used in COVID-19 patients. Tramadol may reduce complications in COVID-19 patients because of its antioxidant property. Not only this, tramadol also provides cardio-protective effect by lowering lactate dehydrogenase (LDH) level significantly. It is seen that in COVID-19 patients, level of T cell is highly reduced as it plays significant role in antiviral immunity. A negative correlation exists in COVID-19 patients between T cell numbers and cytokines serum level, due to which, there is increase in inflammatory cytokines, tumor necrosis factor (TNF)-α. In this condition, administration of 100 mg Tramadol every 12 hours for 10 days decreases TNF-α and increases T cell numbers. It is found that COVID-19 patients having acute respiratory failure and hypercoagulability results in thrombosis. Tramadol due to its hypocoagulable effect can be used in patients having hypercoagulable status and thromboembolic complications [49]. Apart from this, there are several drugs which are under various phases of clinical trial, their mechanism of action, dose and their marketed name is listed in table 2 [50-71].

Convalescent plasma therapy for COVID 19

Convalescent Plasma (CP) therapy includes administration of immunoglobulins containing plasma of a recently recovered individual from COVID 19 to any individual who is susceptible or, infected [72]. Immunized plasma binds with pathogen along with SARS-Cov 2 directly causing it to denature removing it from the peripheral blood stream. Antibody dependent cell-mediated cytotoxicity and phagocytosis also help to achieve the therapeutic effects [73]. In the present situation, human anti-SARS-CoV-2 plasma is the only therapeutic strategy that can be used to prevent and treat COVID-19. Serum IgM and IgA antibody in COVID-19 patients is detected after fifth day of onset of symptoms whereas IgG can be detected from 14th day [74, 75]. From 20th day, IgG can be universally detected [76]. Immunity against other betacoronaviruses lasts from 6-12 months but duration of stay of anti-SARSCoV2 antibodies in plasma is not certain [77]. So a suitable donor can donate 600 ml plasma after every 14 days for a period of 6 months. Single unit inactivation can also be done using a photosensitizer including combination of methylene blue and visible light [78] (Theraflex®), amotosalen (S-59) and ultraviolet A [79] (Intercept®); riboflavin and ultraviolet B [80] (Mirasol®). These processes do not hamper immunoglobulin activity. In 2002 it was found from a study that caprylic acid [81] and octanoic acid [82] were efficient enough to deactivate enveloped viruses. There are several plasma therapies under clinical trial whose details are mentioned in Table 3 [83-102].

Vaccines for COVID 19

Scientists throughout the world have accelerated the process to develop safe and effective COVID-19 vaccines. Vaccines aim to expose the body to an antigen and provoke an immune response that can block or kill the virus if a person becomes subsequently infected, without causing the disease. Various scientific techniques like use of virus vaccines, viral vector vaccine, nucleic acid and protein based vaccines are under development. Many vaccines have already been developed and are under clinical trial is listed in table 4 [103-117].

Table 2. Informations on drugs undergoing clinical trial.

Sr. No.	Drug	Dose	Mechanism	Trade name	Reference
1.	Remdesivir	200 mg (shot) on day 1, followed by 100 mg (shot) daily for 4 days by i.v. route	Remdesivir (GS-5734), a nucleoside analogue prodrug, have inhibitory effects on pathogenic SARS-CoV-2) in vitro.	Veklury, Cipremi	50
2.	Favipiravir	3,600 mg (1,800 mg BID) (Day 1) followed by 1,600 mg (800 mg BID) for up to maximum of 14 days given orally	Favipiravir is a broad-spectrum antiviral drug that selectively inhibits RNA-dependent RNA polymerase (RdRp) as well as viral replication phase of SARS-CoV-2	Avigan	51
3.	Camostat mesylate	600 mg (200 mg, three times) of CM daily	Camostat mesylate (NI-03), a serine protease inhibitor active against TMPRSS2 and inhibits SARS-CoV-2 infection of human lung cells.	Foipan	52
4.	Nafamostat Mesylate	Administered intravenously as a continuous infusion	It blocks SARS-CoV-2 infection of human lung cells with higher efficiency than camostat mesylate	Fusan	53
5.	Baricitinib	4 milligrams (mg) of baricitinib given orally	Oral JAK1/JAK2 inhibitor which blocks host cell proteins responsible for viral reproduction, decreasing infected cells' ability to produce more virus. Restrains immune disregulation in COVID 19 patients	LY3009104	54
6.	Ruxolitinib	5 mg orally every 12 hours during 14 days	Approved for treatment of the myeloproliferative neoplasias polycythaemia vera and primary or secondary myelofibrosis as well as FDA-approved for glucocorticoid-refractory graft-versus-host disease.	Jakafi	55
7.	Carfilzomib	i.v. route 27 mg/m^2	PR-171, is a potent and irreversible epoxomycin-related proteasome inhibitor (1-4). It preferentially inhibits the chymotrypsin-like (CT-L) activity CT-L inhibition with carfilzomib prevents degradation of short-lived misfolded and ubiquitinated proteins intended for proteasomal degradation.	Kyprolis	56, 57
8.	Azvudine	Oral administration of 5 tablets of 1 mg daily	Antiviral, azidocytidine analogue that inhibits viral reverse transcriptase, effective	Azvudine	58
9.	Tocilizumab	i.v in two infusion 12 h apart at 8 mg/kg bodyweight or s.c.at 162 mg in two simultaneous doses	Humanized mAb, IL-6 receptor antagonist, approved by US FDA for treatment of cytokine release syndrome (CRS), caused by COVID-19, thus reducing risk of invasive mechanical ventilation and death in severely affected COVID patients.	Actemra	59
10.	Ivermectin	Ivermectin (0.2 mg /kg) (12 mg /weekly)+ Hydroxychloroquine 400mg/daily + azithromycin 500mg daily	Inhibitor of SARS-CoV-2 virus *in vitro* with a single dose of the drug able to control viral replication within 24 to 48 hours due to inhibition of importin- α/β1 mediated nuclear import of viral proteins. The combination therapy shows better result	Stromectol	60, 61

11.	LY3819253(LY-CoV555)	Administered intravenously	It is a potent, neutralizing IgG1 monoclonal antibody (mAb) effective against the spike protein of SARS-CoV-2, thus blocking viral attachment and entry into human cells which neutralizes the virus responsible for COVID-19.	LY-CoV555	62
12.	Sofosbuvir-Ledipasvir	400 mg Sofosbuvir and 90 mg Ledipasvir, orally once daily for 14 days	Sofosbuvir is an active metabolite with high intracellular stability. SARS-CoV-2 RdRp is very likely to be effectively inhibited by sofosbuvir.	Harvoni	63
13.	Danoprevir+Ritonavir	Danoprevir 100 mg , one tablet twice a day upto 10 days. Ritonavir 100mg, one tablet twice per day upto 10 days.	Danoprevir Hepatitis C virus NS3 protease inhibitor which selectively inhibits HCV replication. It is used in combination with ritonavir.	Roche – Adis Insight	64
14.	Sulodexide	oral dose of 2 capsules each day for 21 days	Sulolodexide is a two-compound drug, each of them with different endothelial action that can be beneficial in COVID-19 patients.	vessel due F	65
15.	Bevacizumab	Bevacizumab 500mg with normal saline 100ml, iv drip ≥90min	Anti-VEGF drug widely used in clinical oncotherapy, is a promising drug for ALI/ARDS in COVID-19 through suppression of pulmonary edema.	Avastin	66
16.	EDP1815 Dapagliflozin Ambrisentan	EDP1815 twice a day for 7 days. Ambrisentan 5mg tablet once daily for 14 days and Dapagliflozin 10mg tablet once a day for 14 days	EDP1815 is an oral formulation containing *Prevotella histicola* isolated from human duodenum. Dapagliflozin is a sodium-glucose co-transporter 2(SGLT-2) inhibitor. Ambrisentan is an endothelin receptor antagonist, and is selective for the type A endothelin receptor (ETA)	Forxiga, Letairis	67
17.	Ravulizumab Baricitinib	Ravulizumab IV (adjusted to weight, Day 1 only) Baricitinib PO OD (4mg, Days 1-14)	Ravulizumab, a monoclonal antibody prevents complement-mediated destruction of cells by binding with C5, terminal complement protein. Baricitinib is licensed for treatment of rheumatoid arthritis, and has the potential to be scaled up for use for a pandemic.	Ultomiris, Olumiant	68
18.	Telmisartan	80 mg Telmisartan twice daily	Telmisartan has a 10-fold higher blocking potency against angiotensin II. It is a partial agonist of PPAR-gamma (Peroxisome Proliferator-Activated Receptor gamma) causing downregulation of AT1 receptor at mRNA and protein level.	Micardis	69
19.	TXA127	0.5 mg/kg intravenously, for 10 days consecutively.	In COVID-19 patients, angiotensin-converting enzyme-2 (ACE-2) is reduced, as a result angiotensin II level increases causing acute kidney injury. Thus administration of TXA127, angiotensin (1-7) replaces levels of ACE-2 and thereby preventing acute kidney injury.	Angiotensin-(1-7)	70
20.	Dornase alpha	2,5 mg/2 times per day for 7 days	Pulmozyme contains an active substance called dornase alpha. It reduces the viscosity and quantity of airway mucus in Cystic Fibrosis (CF) patients. The similarity of mucus secretions in COVID-19 and cystic fibrosis patients by the means of NETs makes Dornase alfa as a therapeutic option in COVID-19.	Pulmozyme	71

Table 3. Recent report on clinical trial on plasma therapy for Covid 19.

Sr. No.	Name of study	Phase	Start date	End date	No. of patient, location	Dose	Stage	Reference
1.	Hyperimmune Plasma in Patients With COVID-19 Severe Infection (COV2-CP)	Phase 2 Phase 3	May 1	May 15, 2021	400, Italy	Administration of hyperimmune plasma on day 1 and on day 3 and 5 on the basis of clinical response	Recruiting	83
2.	COVID-19 Convalescent Plasma (CCP) Transfusion	Early Phase 1	June 1	May 31 2022	100, Mississippi, US	One unit of Convalescent Plasma transfused	Recruiting	84
3.	Safety and Efficacy of Convalescent Plasma Transfusion for Patients With COVID-19 (EPCOvid-1)	Phase 2 Phase 3	Aug 25	Dec 31	410, Mexico	Two 200 ml infusions will be administered with 24-72 hours in between.	Recruiting	85
4.	Convalescent Plasma for Treatment of COVID-19: An Exploratory Dose Identifying Study	Phase 1 Phase 2	May 2020	December 2020	50, Sweden	Treatment with convalescent plasma (200ml, up to a maximum of 7 CP infusions).	Recruiting	86
5.	Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease (CONCOVID Study) (ConCoVid-19)	Phase 2 Phase 3	April 8	July 1	426, Netherland	300mL of convalescent plasma	Recruiting	87
6.	Convalescent Plasma of Covid-19 to treat SARS-COV-2 a Randomized Double Blind 2 Center Trial (CPC-SARS)	Phase 2	May 20	July 20	80, Mexico	Hyperimmune Plasma from Convalescent patients and conventional Therapy (Azithromycin and Hydroxychloroquine)	Recruiting	88
7.	Safety in Convalescent Plasma Transfusion to COVID-19	Phase 1	May 8	April 30	20, Mexico	Convalescent Plasma from patients who recently recover from COVID-19	Recruiting	89
8.	Convalescent Plasma as Treatment for Hospitalized Subjects With COVID-19 Infection	Phase 2	April 2020	April 2021	55, United States, New Jersey	Fresh or frozen plasma will be infused one time to hospitalized patients with COVID-19 infection	Recruiting	90
9.	Convalescent Plasma to Limit COVID-19 Complications in Hospitalized Patients	Phase 2	April 2020	August 2023	300, US	1-2 units of volume 250-500 mL	Recruiting	91
10.	Convalescent Plasma for the Treatment of COVID-19		April 2020	April 2021	100, US	200-600 milliliters of convalescent plasma	Recruiting	92
11.	Efficacy of Convalescent Plasma Therapy in the Early Care of COVID-19 Patients.	Phase 3	May 2020	Oct 2020	80, France	2 Convalescent Plasma units of 200-230mL each, inactivated by amotosalen.	Recruiting	93

12.	Treatment of Patients With COVID-19 with Convalescent Plasma (COOPCOVID-19)	Phase 2	June 2020	May 2022	120, Brazil	1:1:1 into 3 treatment groups: A- standard (control); B- standard and convalescent plasma of 200ml volume; C- standard and convalescent plasma of 400ml volume	Recruiting	94
13.	Hyperimmune Convalescent Plasma in Moderate and Severe COVID-19 Disease	Phase 2	May 1	Sep 15	60, Russia	300 ml plasma on day 1 and day 2	Recruiting	95
14.	Convalescent Plasma for COVID-19 Close Contacts	Phase 2	May 2020	April 2021	200, New York	1 unit of approximately 200 to 250 mLvolume	Recruiting	96
15.	Early transfusIon of Convalescent Plasma in Elderly COVID-19 Patients. to Prevent Disease Progression. (LIFESAVER)	Phase 2 Phase 3	May 2020	June 2021	182, Italy	200 ml/day for 3 days (days 1, 2, and 3).	Recruiting	97
16.	Efficacy and Safety of Early COVID-19 Convalescent Plasma in Patients Admitted for COVID-19 Infection	Phase 2	May 4	Aug 17	58, India	200 ml day 1 and 2 only if respiratory function or COVID symptoms worsens for more than 7 days after enrolment	Completed	98
17.	Potential Efficacy of Convalescent Plasma to Treat Severe COVID-19 and Patients at High Risk of Developing Severe COVID-19	Phase 2	April 2020	April 2021	575, Saudi Arabia	10-15 ml/kg body weight at least once & if possible, daily, for up to 5 sessions.	Recruiting	99
18.	A Clinical Trial of Convalescent Plasma Compared to Best Supportive Care for Treatment of Patients With Severe COVID-19 (CAPSID)	Phase 2	June 2020	Feb 2021	106, Germany	Convalescent plasma transfusion on day 1, 3 and 5.	Recruiting	100
19.	Efficacy of Convalescent Plasma Therapy in Patients With COVID-19	Phase 3	June 2020	May 2021	400, India	250 ml/ day for two days from day 3 of symptom onset	Recruiting	101
20.	Assess the Safety and Efficacy of Convalescent Plasma to Limit COVID-19 Associated Complications	Phase 2	May 2020	Aug 2021	100, India	200 ml of ABO compatible plasma transfusion will be done	Recruiting	102

Table 4. Recent report on clinical trial on vaccines for Covid 19.

Sr. No.	Name of study	Phase	Start date	End date	No. of patient, location	Dose	Stage	Reference
1.	Clinical Trial of Efficacy and Safety of Sinovac's Adsorbed COVID-19 (Inactivated) Vaccine in Healthcare Professionals (PROFISCOV)	Phase 3	July 2020	October 2021	8870, Brazil	Two dose of intramuscular injections (deltoid) with an interval of 14 days.	Recruiting	103
2.	A Clinical Trial of a Recombinant Adenovirus 5 Vectored COVID-19 Vaccine (Ad5-nCoV) With Two Doses in Healthy Adults	Phase 1	September 2020	June 2021	168, China	Intramuscular vaccination and mucosal vaccination of two doses in different administration schedules	Recruiting	104
3.	BCG Vaccine in Reducing Morbidity and Mortality in Elderly Individuals in COVID-19 Hotspots	Phase 3	July 2020	May 2021	2175, India	One dose of 0.1ml BCG vaccine, given intradermally	Recruiting	105
4.	Monovalent Recombinant COVID19 Vaccine (COVAX19)	Phase 1	July 2020	October 2021	40, Australia	Spike antigen (25ug) with 15 mg Advax-2 adjuvant	Recruiting	106
5.	Efficacy, Safety and Immunogenicity Study of SARS-CoV-2 Inactivated Vaccine (COVID-19)	Phase 3	August 2020	September 2021	1620, Indonesia	2 doses of inactivated vaccine intramuscularly with 14 days interval	Recruiting	107
6.	An Open Study of the Safety, Tolerability and Immunogenicity of the Drug "Gam-COVID-Vac" Vaccine Against COVID-19	Phase 3	June 2020	August 2020	38, Russia	Intramuscular administration once	Completed	108
7.	SCB-2019 as COVID-19 Vaccine	Phase 1	June 2020	March 2021	150, Australia	Intramuscular vaccinations of volume 3 µg- 30 µg twice (on Day 1 and Day 22).	Recruiting	109
8.	Evaluation of the Safety and Immunogenicity of a SARS-CoV-2 rS Nanoparticle Vaccine With/Without Matrix-M Adjuvant	Phase 1 Phase 2	July 2020	October 2021	1631, United States	2 doses of SARS-CoV-2 rS - 25 µg, 1 dose each on Days 0 and 21.	Recruiting	110
9.	Safety, Tolerability, and Pharmacokinetics of SAB-185 in Ambulatory Participants With COVID-19	Phase 1	August 2020	December 2020	21, United States	SAB-185 of 10, 25, 50 mg/kg in normal (0.9%w/v) saline	Recruiting	111
10.	Study of COVID-19 DNA Vaccine (AG0302-COVID19)	Phase 1 Phase 2	July 2020	October 2021	30, Japan	2.0 mg of AG0302-COVID19 twice at 2-week intervals, 4 weeks interval	Recruiting	112
11.	A Study to Evaluate The Efficacy, Safety and Immunogenicity of Inactivated SARS-CoV-2 Vaccines (Vero Cell) in Healthy Population Aged 18 Years Old and Above (COVID-19)	Phase 3	July 2020	September 2021	45000, UAE	2 doses of the inactivated SARS-CoV-2 vaccine (Vero cell) on day 2 and day 21	Recruiting	113

12.	Immunity and Safety of Covid-19 Synthetic Minigene Vaccine	Phase 1 Phase 2	March 2020	December 2024	100, China	5x10^6 LV-DC vaccine and 1x10^8 CTLs via sub-cutaneous injections and iv infusions, respectively.	Recruiting	114
13.	Safety and Immunity of Covid-19 aAPC Vaccine	Phase 1	February 2020	December 2024	100, China	Three injections of 5x10^6 each Covid-19/aAPC vaccine (artificial antigen presenting cells) via subcutaneous injections.	Recruiting	115
14.	A Study to Evaluate the Safety, Reactogenicity and Immunogenicity of Vaccine CVnCoV in Healthy Adults	Phase 1	June 2020	August 2021	168, Germany	Intramuscular injection by at escalating dose levels 2, 4 and 8 μg on Day 1 and Day 29.	Recruiting	116
15.	A Study to Assess Safety, Tolerability, and Immunogenicity of V591 (COVID-19 Vaccine) in Healthy Participants (V591-001)	Phase 1 Phase 2	August 2020	April 2022	260, Belgium	1 or 2 ascending doses of V591 will be administered via intramuscular (IM) injection.	Recruiting	117

Conclusion

From December 2019 on, the worldwide outbreak of COVID-19 has affected almost all the countries. At present, owing to its broad clinical scope, there are no clear therapeutic agents for this condition but numerous drugs, vaccines as well as human convalescent plasma have been under clinical trial throughout the world since the inception of this outbreak till date. The alarming reports of WHO for COVID 19 cases and death rates over the whole world is putting a pressing need for the development of effective drug and vaccine to control this deadly pandemic. The only FDA-approved drug is remdesivir. Many entities have shown adequate indication and promising response and thus can be a potential strategy towards this deadly disease and are under clinical trial but it will require certain time to approve and market the safe and immunogenic vaccine. The findings of good clinical trials on certain drugs and promising vaccines can prove to be boon for combating COVID-19 to narrow down the devastating effects of this global pandemic.

Conflicts of Interest

The authors declare no conflict of interest.

Author contributions

All the authors have contributed equally in designing, drafting the manuscript as per the journal submission format. All authors read and approved the final manuscript.

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