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Review Article

Progress in the Development of Potential Therapeutics and Vaccines against COVID-19 Pandemic

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19 or coronavirus disease 2019 and the same has been declared as a global pandemic by WHO which marked the third introduction of a virulent coronavirus into human society. This is a highly pathogenic human coronavirus in which pneumonia of unknown origin was identified in China in December 2019 and is a threat to human life worldwide. Considerable efforts have been made for developing effective and safe drugs and vaccines against SARS-CoV-2. The current situation and progress in the development of various therapeutic candidates including vaccines in preclinical and clinical studies have been described in the manuscript. Until now, many people have been infected with this lethal virus, and a lot of people have died from this COVID-19. This viral disease spreads by coming in contact with an infected person. Understanding of SARS-CoV-2 is growing in relation to its epidemiology, virology, and clinical management strategies. Till date, very few drugs or vaccines have been developed or approved for the treatment of this deadly disease of COVID-19 and many candidates are under the clinical development pipeline. Apart from the fact that our knowledge has risen well beyond the two precedents of coronavirus, there is still a wide loophole in the successful exploration of the therapeutic strategies and management of the outbreak of this virus. Moreover, successful integration of the outcomes from different *in vivo* evaluation and *in silico* studies including vaccine development strategies could be a great tool in the discovery of safe and effective treatment strategies. Although, vaccines have shown tremendous potential to combat the current pandemic situation but a vaccine candidate(s) effective in discrete phases of the pandemic is highly desirable. Currently, more than 250 vaccine candidates are under preclinical and clinical developmental pipeline, but there are stringent challenges that need to be addressed especially the unknowns about the disease. This review summarizes the various therapeutic targets and strategies for the treatment of SARS-CoV-2 infection including the status of various small molecules as well as potential vaccine candidates under clinical development.

Keywords: COVID-19; SARS-CoV-2; Coronavirus; Vaccines; Clinical Trials; Repurposing; Diagnostics

Introduction

One of the massive eruptions towards mankind in 2019–2020 is the outbreak associated with the corona virus in China and now throughout the world. Globally, there is tremendous stress upon the health care systems and societies which can be realized from its prevailing patterns in the past few months [1,2]. The first outbreak of the SARS (severe acute respiratory syndrome) was earlier identified in 2002-2003 Guangdong province, China. This virus caused mild infections in immunocompetent people [3]. Ten years after SARS, another outbreak of coronavirus was caused named

Middle East respiratory syndrome coronavirus (MERS-CoV) in Middle Eastern countries. Studies have shown that MERS-CoV infects unciliated bronchial epithelial cells and type II pneumocytes by utilizing dipeptidyl peptidase 4 (DPP4) as the functional host receptor [4]. After these two outbreaks, another coronavirus came into the existence named as SARS-Cov-2 or COVID-19 and it is the third zoonotic disease of coronavirus. COVID-19, characterized by severe pneumonia condition is an infectious disease that originated from Wuhan city, Hubei province, China. Initially, WHO (World Health Organisation) named COVID-19 as 2019-novel coronavirus (2019-nCov) and then named it coronavirus disease-2019 (COVID-19) [5]. On 30th Janaury2020, WHO declared Covid-19 as World health emergency. Further, Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses named COVID-19 as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [6]. SARS-Cov-2 is the coronavirus that belongs to β-coronavirus which is one of the four genera of coronavirus and further it was confirmed that β-coronavirus belongs to the subgenus botulinum of Coronaviridae [7]. The first case of COVID-19 was reported on 31st Dec 2019 and according to WHO, 89,707,115 million people are infected with this disease globally including 1,940,352 deaths as of 12th Jan 2021 [8].

The epidemiological and clinical characteristics of SARS-CoV-2 indicate that this new outbreak is different from the 2003-SARS outbreak. Several symptoms like headache, nasal congestion, sore throat, myalgia, and arthralgia are common symptoms in the patient who is infected with COVID-19. Diarrhoea, vomiting, and nausea are the few other minor symptoms noticed among the infected children. Some of the severe conditions like acute cardiac injury, acute kidney injury, shock, sepsis, mental status, low oxygen saturation, reduced urine output, weak pulse, cold extremities, low blood pressure, mottled skin, and even multi-organ dysfunction are also seen in the patients suffering from COVID-19 infection [9]. Like influenza, coronavirus (CoV) spreads via respiratory droplets and interpersonal contact, therefore it is advisable to avoid presence in crowded places to minimize the risk of transmission of infection [10,11]. On the other hand, in November 2020 two new mutated strains of COVID-19 were found. The first strain was reported in the United Kingdom by the University of North Carolina and the University of Wisconsin-Madison. In their report, they had reported that the D614G strain of COVID-19 was more dangerous as it is replicate faster. The other strain of COVID-19 was found in South Africa and like UK it is also more problematic as compared to the previous strains [10]. The second wave of the pandemic that hit Brazil has been far worse, with the country recording more than 70,000 cases and around 2,000 deaths daily. According to Johns Hopkins University of Medicine data, Brazil registered 4,75,503 new cases and 11,009 deaths within a week — both a record high. On March 10, the country recorded 2,286 Covid deaths, the highest in a day so far, the Reuters reported. It also recorded close to 80,000 fresh cases. Experts have attributed the surge in the number of cases and deaths to a more contagious variant of the virus, P.1, which is also known as the Brazil variant. The P.1 variant, which had swept through Manaus, capital of the northern state of Amazonas, is more infectious and does not spare people who have already suffered from Covid earlier. The P.1 strain is being considered to be a variant of particular concern, alongside the mutant strains that have emerged from the United Kingdom and South Africa. Genomic surveillance carried out by a team of researchers from Brazil following the outbreak in Manaus found that the P.1 lineage carries a collection of mutations which are located in the spike protein receptor binding domain, the region of the virus involved in recognition of the angiotensin-converting enzyme-2 receptor. By the end of February, the P.1 variant had spread to 21 of the 26 Brazilian states. The mutant strain can be twice as transmittable as the original virus and can also evade immunity in people who have developed antibodies after being infected earlier. This makes the disease more deadly and requires immediate focus on the development of safe and effective treatment strategy [11]. The scope of this review is to discuss the recent developments related to the identification of various therapeutic drug targets, diagnostic tools, and potential therapeutic agents against COVID-19. Further, this review will also shed light upon the development status of various drug candidates which are under the different stages of clinical trials.

Genome, protein, and structure of COVID-19 related to coronavirus

The genome of coronaviruses ranges from 27 to 32 Kb in length is a single-stranded positive-sense RNA which is the largest amongst the RNA viruses [12]. All the known coronaviruses consist of four main structural proteins named spike (S), envelope (E), membrane (M), and nucleocapsid (N) [12,13]. The S protein comprised of two subunits i.e. S1 and S2, facilitate the virus entry into host cells through a defined receptor-binding domain (RBD) (ACE2

for COVID 19) which is located on the S1 subunit followed by the fusion of viral and host membranes via S2 subunit. The process is further facilitated by the host cell proteases (Figure 1) [14]. The S1 subunit is located at the N-terminus which possesses receptor binding function while the S2 subunit is located at the C-terminus responsible for presuming the fusion activity. In the case of CoVs, the S-protein belongs to class I fusion protein which ranged from simple sugars to complex proteins. Besides this much structural complexity and diversity of functions, only about one-third of the coding capacity of the genome was occupied by the structural proteins of CoVs [15]. About two-third portion of the genome sequence is located at the 5'-end, which encodes for two open reading frames i.e., 1a and 1b. Various non-structural proteins of the virus are encoded by both of the frames (1a and 1b) together. Initially, each sequence is translated as a polyprotein precursor, pp1a and pp1ab, which encodes different viral proteases that mediate the processing of pp1a and pp1ab into 16 non-structural proteins (nsp1–16), which are necessary at several stages of the virus replication cycle [16]. The viral surface proteins, S, M, and E come across cellular membranes at the beginning of the infection. These virus surface proteins translated and the replicated proteins are then incorporated into the endoplasmic reticulum and endoplasmic reticulum Golgi intermediate compartment and also in the secretory pathway where mature virions are formed by the budding process [17]. As in the case with other positive-stranded RNA viruses, various non-structural proteins also interact with the membranes. Hence, virus replication occurs in specific cellular sections which are induced by viral proteins that change the host membranes or organelles to set up specialized sites for the viral replication that remained hidden from the components of the inherent immunity [18]. CoVs represent one of the aggrandized challenging virus-membrane interaction models due to the augmentation of diverse interacting factors and multiple sites of interaction present within the viral membrane [19]. Studies revealed that the amplest and conserved SARS-CoV 2 protein showed almost 90% similarity with the N protein of SARS-CoV while the genome of SARS-CoV 2 showed 80% similarity to the SARS-CoV at the nucleotide level. The attachment or strong interaction between the COVID-19 S-protein and human ACE-2 receptor molecules supported the fact of COVID-19 transmission to humans via the S protein–ACE-2 interaction pathway. ACE-2 is cleaved by a protease named TMPRSS2 (Transmembrane Serine *Protease* 2) to facilitate the virus entry into the host cell [20].

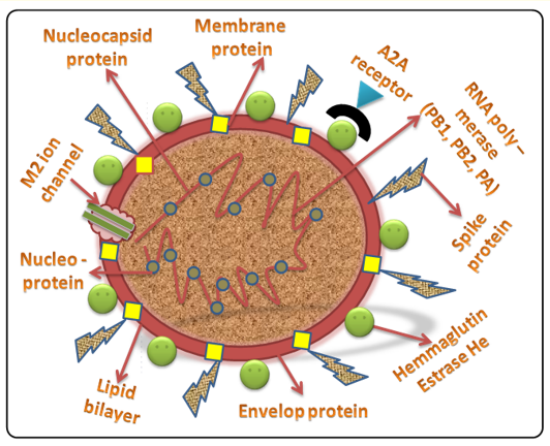

Figure 1: Structural components of the SARS-CoV-2 virus.

Diagnostics to detect COVID-19

After the arrival of this pandemic, various laboratories across the globe started developing the kits or tools to diagnose the nCoV-2. Various countries like United State (US), India, Korea, and China are the few major countries which have initiated and developed diagnostic kits. US-based laboratories like Medtech, Biomednomics, and CTK Biotech have developed a diagnostic kit for the detection of COVID-19 and it has received an acknowledgment from the US food and drug administrator (USFDA) [21,22]. German-based company Bosch has also developed a diagnostic kit for the detection of COVID-19 in just six weeks. Sugentech is a Korean-based laboratory that has also developed the kit for the detection of COVID-19. Getein biotech, Hangzhou biotest biotech, Amonmed biotechnology co., Beijing tigsun diagnostics co ltd, Hunan lituo biotechnology co., Vivacheck lab, and Wondfo are the China-based laboratories that have developed diagnostic kits for COVID-19. Biomaxima is the Poland-based laboratory that successfully developed a diagnostic kit for the COVID-19. Singapore-based company Sensing self ltd. has also developed a diagnostic kit for the detection of COVID-19 infection whereas, the India-based Mylab laboratory has also developed a diagnostic kit for the detection of COVID-19 [23]. Diagnostic kits of different countries to diagnose COVID-19 are given in table 1.

Therapeutic agents for the treatment of COVID-19

The rapid spread of COVID-19 augments the urgent need for the development of effective therapeutic strategies against

Sr. No.	Country	Laboratories/Companies
1.	China	Getein biotech, Hangzhou biotest biotech, Amonmed biotechnology co., Beijing tigsun diagnostics co ltd, Hunan lituo biotechnology co., Vivacheck lab, Wondfo lab
2.	USA	Medtech, Biomednomics, CTK Biotech
3.	Germany	Bosch
4.	Korea	Sugentech
5.	Poland	Biomaxima
6.	Singapore	Sensing self ltd
7.	India	Mylab

Table 1: List of kits available to diagnose COVID-19.

SARS-CoV-2. Based upon the previous knowledge associated with the treatment of influenza, Ebola, MERS, SARS, and other viral infections, various types of drugs are currently being used for the treatment of COVID-19 and a lot of research efforts are currently focused on drug repurposing. Drugs belonging to different classes having the potential against COVID-19 are discussed below and shown in figure 2.

RNA-dependent RNA polymerases inhibitors

Remdesivir is an inhibitor of RNA-dependent RNA polymerases (RdRps) and is a far most promising drug candidate which possesses a broad spectrum of antiviral activities against a panel of RNA viruses. It is a monophosphoramidate prodrug of an adenosine analog whose active form is incorporated into RDRP thereby causing the rarest of RNA synthesis. Various *in vitro* and *in vivo* research findings have proven the antiviral potential of remdesivir against a range of viruses including SARS-CoV and MERS-CoV [24]. Remdesivir displayed excellent *in vitro* activity against both the coronaviruses (MERS-CoV and SARS-CoV) with EC_{50} values of 0.07 µM, whereas it has an EC_{50} value of 1.76 µM against COVID-19, measured in infected Vero E6 cells [25]. Clinical study results depicted that Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with Covid-19 and evidence of lower respiratory tract infection. (ClinicalTrials.gov number, NCT04280705). On October 22, 2020, FDA approved Veklury (remdesivir) for use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. Veklury should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care.

Favipiravir and ribavirin are the other potential drugs belonging to this which are monophosphoramidate prodrugs of guanine analogs. Favipiravir was developed by Toyama Chemical (a division of Fujifilm), Japan, and act by inhibiting the enzyme RNA-dependent RNA polymerase (rdrp) due to its structural resemblance with the endogenous guanine base [26]. It has been approved for the treatment of COVID-19 in some countries including India but it is less efficient as compared to Remdesivir (Figure 2). Favipiravir has a teratogenic potential and embryotoxicity side effects which makes its use limited. The Japanese drug safety bureau approval advises that favipiravir be given a strong warning against use in women of reproductive age and recommends precautionary statements on packaging and prescription alerts [27].

Viral protease inhibitors

FDA-approved Ivermectin is an anti-parasitic agent and the therapeutic potential of this drug has also been established as an antiviral agent against both human immunodeficiency virus (HIV) and dengue virus. It acts by inhibiting the viral protease enzyme crucial for the production of viral proteins. Targeting the nuclear transport process may be a feasible therapeutic approach toward RNA viruses as nuclear transport of viral proteins is requisite for the replication cycle as well as for the suppression of the host's immune response. The therapeutic potential of Ivermectin to reduce the viral RNA up to 5,000-fold after 48 h of infection with SARS-CoV-2 has been explored in a recent *in vivo* study [28,29]. It was also established that Lopinavir/Ritonavir can be used in combination for the treatment of COVID-19. The retroviral aspartyl protease enzyme plays an indispensable role in the viral replication pathway, encoded by the pol gene in the human immunodeficiency virus (HIV), and facilitates the cleavage of precursor polypeptides into smaller proteins. Lopinavir and ritonavir are the inhibitors of HIV protease and are used in combination for the treatment of HIV infection. Coronavirus has encoded with the different enzymatic class of protease, the cysteine protease, and there is evidence that has shown the ability of lopinavir and ritonavir to inhibit the coronavirus main proteinase 3C-like protease (3CLpro). The processing of the polypeptide translation product from the genomic RNA into

the protein constituents is mediated by 3CLpro [30]. It is worth mentioning that a number of *in vitro* and clinical investigations confirmed the antiviral potential of these candidates against the SARS and MERS viruses with EC_{50} values 17.1 and 8 μM, respectively. But clinical studies revealed that the combination has not shown any significant therapeutic effect in treating severe illness caused by SARS-CoV-2.

Further, interferon β-1β was found to be efficient inhibitors of multiplication of SARS-CoV and MERS-CoV and the combination of Lopinavir/Ritonavir with interferon β-1α was also tested and found to expedite the recovery, suppress the viral load, shorten hospitalization and reduce mortality in patients with 2019-n-CoV infection compared to lopinavir/ ritonavir. (ClinicalTrials.gov Identifier: NCT04276688). Further, it was established that SARS-CoV-2 utilizes the ACE2 receptor for the entry and host cellular serine protease TMPRSS2 for the S protein priming. Thus, a potential approach for the treatment of COVID-19 can be developed by targeting the potential interactions between ACE2 and S-protein. These interactions can be inhibited by clinically proven TMPRSS2 inhibitor camostat mesylate which significantly reduced the lung cell line infection with SARS-CoV-2 (Figure 2). The Impact of Camostat Mesylate on COVID-19 Infection (CamoCO-19) has been studied in a clinical trial [ClinicalTrials.gov Identifier: NCT04321096] whose results showed its efficacy in reducing the mortality rate.

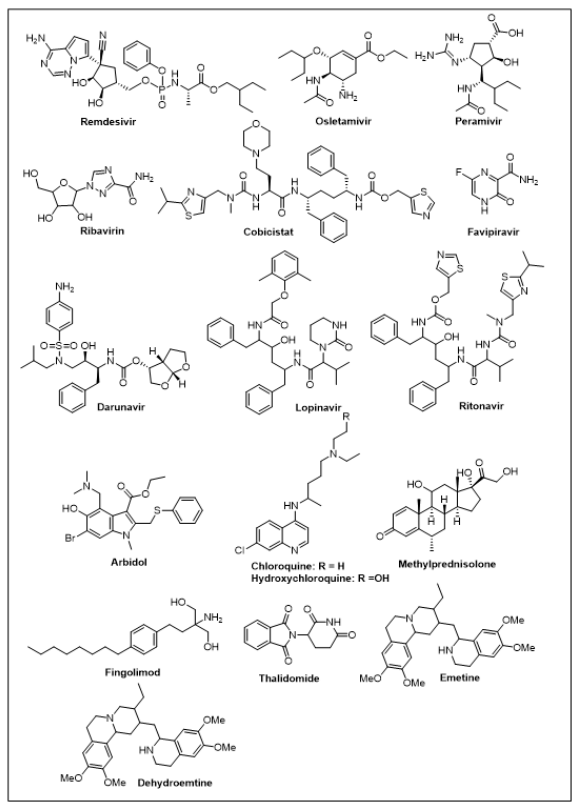

Figure 2: Structure of various effective therapeutic agents against COVID-19.

Blocker of virus-cell membrane fusion

Hydroxychloroquine and chloroquine are the re-known antimalarials with anti-autoimmune properties. They also possessed the ability to block the viral infection by increasing the endosomal pH required for the fusion between the host and virus-cell membranes. Apart from this, both drugs interfere with the glycosylation of its cellular receptor, ACE2, thereby inhibiting the replication of SARS-CoV. Furthermore, some of the SARS-CoV-2 clusters can use ACE2 receptors for entry into the host cell as shown by the outcome of sequence analysis data. Thus, targeting of ACE2 represents a validated therapeutic approach to prevent or combat the infection caused by SARS-CoV-2. In a study, both chloroquine and hydroxychloroquine were found to inhibit MERS with EC_{50} values 6.54 and 7.97 μM and SARS with EC_{50} values 6.28 and 8.28 μM, respectively. Against the COVID-19, chloroquine and hydroxychloroquine have EC_{50} values of 5.47 and 0.72 μM, respectively. Moreover, few reports claimed that hydroxychloroquine and chloroquine effectively reduced the viral copy number of SARS-CoV-2. As a result, rapid clinical trials were conducted in China which established the effectiveness of both the drugs to certain degrees for the treatment of pneumonia associated with COVID-19 [31]. To check the efficacy of hydroxychloroquine on clinical status in 14 days in hospitalized patients with COVID-19, a randomized clinical trial was conducted which revealed that among adults hospitalized with respiratory illness from COVID-19, treatment with hydroxychloroquine, compared with placebo, did not significantly improve clinical status at day 14. Hence, these findings do not support the use of hydroxychloroquine for the treatment of COVID-19 among hospitalized adults. (ClinicalTrials.gov: NCT04332991). Therefore, hydroxychloroquine was terminated from the clinical trials for further development against Covid-19 [31].

Arbidol Hydrochloride is a Russia-made powerful broad-spectrum antiviral which is used for the treatment of a number of enveloped and non-enveloped viruses. The drug is majorly used in Russia and China and is effective in treating influenza A and B viruses and hepatitis C virus. The entry of the viruses like influenza virus and arbovirus was inhibited by arbidol by the targeting of hemagglutinin (HA, the major glycoprotein on the surface of the influenza virus), thereby preventing the fusion between the endosome and the viral membrane after endocytosis. Due to the increasing pandemic situation, the surge for effective therapeutic resulted in the use of arbidol as a therapeutic regime. Thus, the National Health Commission of China, in February 2020 issued guidance selecting Lopinavir-ritonavir and arbidol for treating COVID-19. The decision for the selection was based on in-vitro cell tests and previous clinical data from SARS and MERS. This further led to an increase in the production of arbidol hydrochloride in China. Various clinical trials have been undertaken to discover the effectiveness of arbidol against COVID-19 [32]. Using an open-label randomized controlled trial, the efficacy of ARB was examined in patients with COVID-19 in a hospital. One hundred eligible patients with the diagnosis of COVID-19 were recruited in the study and assigned randomly to two groups of either hydroxychloroquine followed by KALETRA (Lopinavir/ ritonavir) or hydroxychloroquine followed by ARB. The primary outcome was hospitalization duration and clinical improvement 7 days after admission. The criteria for improvement were relief of cough, dyspnea, and fever.

Attenuator of the inflammatory response

A higher concentration of cytokines was claimed in the plasma of patients in the intensive care unit (ICU) compared to non-ICU patients infected with COVID-19, thereby suggesting that host inflammatory response such as cytokine outburst in infection was involved in disease severity. Hence, inhibition of excessive inflammatory response represents a valuable approach for treating severe complications in COVID-19. Thalidomide has been re-purposed as an anti-fibrotic, anti-inflammatory and antiangiogenic agent in recent reports. Its ability to decrease the synthesis of TNF-α made it useful for the treatment of multiple inflammatory diseases like Crohn's disease and Behcet's disease. Literature reports claimed that thalidomide was effective in reducing the infiltration of inflammatory cells as well as the production of pro-inflammatory cytokines in H1N1-infected mice. Considering the immunomodulatory effect of thalidomide, clinical trials were initiated in China to lessen the burden of lung injury caused by an excessive immune response to COVID-19 [33]. Recently, thalidomide in combination with low-dose glucocorticoid has shown beneficial outcomes in a patient with severe COVID-19 pneumonia. However, more supportive data from preclinical and well-designed clinical studies are required to establish the effectiveness of thalidomide for treating COVID-19. Methylprednisolone is a glucocorticoid and a well-known immunosuppressant. The direct damage caused by the virus and overexpressed immune system of the host had led to the development of pneumonia in the COVID-19 patients. Thus, it was thought that the administration of methylprednisolone would help in suppressing unwanted immune reactions. Currently, the studies are ongoing to establish the effectiveness and safety of this drug as a recent study claimed the benefits of corticosteroid treatment in a subset of severely ill patients with SARS-CoV-2 [34]. Fingolimod is an oral immune-modulating agent derived from myriocin and majorly used as a first-line agent for the treatment of refractory multiple sclerosis. It acts as a highly potent functional antagonist of sphingosine-1-phosphate (S1P1) receptors in the lymph node T cells due to its structural resemblance with sphingosine-1-phosphate (S1P). S1P1 receptors are internalized and the lymph nodes T-cells are subsequently sequestered through effective binding. Thus, it presents a valuable approach to attenuate the uncontrolled immunopathogenesis related to COVID-19 figure 2 [35].

Controlling the symptomatic (VEGF Inhibitors)

Vascular endothelial growth factor (VEGF) mediates the induction of endothelial injury, increases the microvascular permeability and elevated levels of VEGF are observed in the patients suffering from acute respiratory distress syndrome. Bevacizumab is a well-known anti-VEGF recombinant humanized monoclonal antibody widely used for the treatment of several cancers. It has the capability of blocking angiogenesis by specific binding to VEGF (Figure 2). A recent study with 26 patients recruited from 2-centers (China and Italy) claimed that bevacizumab showed clinical efficacy in patients with severe COVID-19 by improving oxygenation and shortening oxygen-support duration as compared to the control patients [36]. Various clinical studies are ongoing to evaluate the effectiveness of bevacizumab to treat COVID-19 being currently in phase 2 of clinical trials.

Nucleoside analogues

Nucleoside analogues are the prodrugs that underwent phosphorylation inside the cells to the active nucleotide analogues which

then act as a potent inhibitor of the essential viral enzyme, DNA polymerase [37]. Ribavirin is a nucleoside analogue which in combination with broad-spectrum antiviral agents or recombinant interferon used for the treatment of MERS-CoV (Figure 2). A combination of interferon β-1b and ribavarin has been in phase 2 of clinical trials (last updated July 31, 2020 - ClinicalTrials.gov Identifier: NCT04494399) for treatment against COVID-19. The Chinese National Health Commission also recommended an intravenous infusion of ribavirin in combination with inhaled interferon-α or oral lopinavir/ritonavir for the treatment in the newest guideline on COVID-19. But military medical has not recommended the ribavirin and there is a risk of virus-containing aerosol production and airway stimulation by the administration of interferon-α inhalation [38].

Neuraminidase inhibitors

Oseltamivir and Peramivir are the neuraminidase inhibitors (NAIs) used for the improvement in influenza patients. Mechanism of action associated with the neuraminidase inhibitors involved blockage of the active site of neuraminidase and leave uncleaved sialic acid residues on the surfaces of host cells. Oseltamivir is also used for confirmed as well as suspected COVID-19 patients. Oseltamivir along with hydroxychloroquine and azithromycin combination has been under phase 3 clinical phases which has been proven to effective in clearing the coronavirus and improving the clinical course of the diseases [39]. (ClinicalTrials.gov Identifier: NCT04338698).

3C-like protease (3CLpro) inhibitors

3CLpro is one of the most vital proteases for RdRP generation, virus replication, infection, and responsible for processing the polypeptide translation product from the genomic RNA into the protein components. The antiretroviral drugs lopinavir and ritonavir target the coronavirus main proteinase (3C-like protease; 3CLpro) and proved to be effective in patients infected with SARS-CoV. 3C-like protease (3CLpro) inhibitors like darunavir and cobicistat (Figure 2) are currently undergoing phase 3 of clinical trial against COVID-19 [40]. The randomised evaluation of COVID-19 therapy (RECOVERY) trial is an ongoing, open-label, randomized controlled trial with multiple arms, including a control arm; in one arm, participants received lopinavir/ritonavir. The trial was conducted across 176 hospitals in the United Kingdom and enrolled hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection. Patients were randomized into several parallel treatment arms; this included randomization in a 2:1 ratio to receive either the usual standard of care only or the usual standard of care plus lopinavir 400 mg/ritonavir 100 mg orally every 12 hours for 10 days or until hospital discharge. Patients who had severe hepatic insufficiency or who were receiving medications that had potentially serious or life-threatening interactions with lopinavir/ritonavir were excluded from randomization into either of these arms. Mechanically ventilated patients were also underrepresented in this study because it was difficult to administer the oral tablet formulation of lopinavir/ritonavir to patients who were on mechanical ventilation. The primary outcome was all-cause mortality at day 28 after randomization. The lopinavir/ritonavir arm was discontinued on June 29, 2020, after the independent data monitoring committee concluded that the data showed no clinical benefit for lopinavir/ritonavir [41].

Herbal drugs as effective agents

An essential alkaloid emetine, present in the root of plant ipecacuanha (ipecac) and syrup of ipecac has mostly been used for the management of poisoning by inducing vomiting. As an antiviral agent, emetine has shown EC_{50} values of 0.054 and 0.014 μM against MERS and SARS, respectively, and also higher concentration of drugs were identified in the lungs than the plasma [42]. In this regard, emetine and its analogue like dehydroemetine can be examined as a potential lead for the development of new drug candidate(s) against the coronavirus in combination with serotonin 5-HT_3 antagonists (such as ondansetron) to reduce the emetic effect associated with the administration of emetine. The utility of emetine and its analogues for the potential treatment of COVID-19 is yet to be established. Besides, Traditional Chinese medicine (TCM) such as liquorice roots (containing Glycyrrhizin), baicalin, *Radix Scutellaria* (flavonoid containing drug), and many others have been proven effective against SARS-CoV and MERS-CoV. These drugs could also be explored for the potential treatment of COVID-19 [43]. The products from TCM like ShuFeng JieDu and Lianhua Qingwen capsules have shown beneficial effects to treat effective influenza antiviral effects and also displayed very promising synergistic antiviral effects with the use of Western medicine products. The patented TCM medicines like Shufengjiedu capsule and Jinhuaqinggan granules were recommended according to the Chinese national guidance as a treatment regime against COVID-19. These formulations were prepared using various plant

extracts through TCM which finds application in the treatment via multiple signaling pathways. Shufengjiedu capsule mainly targeted ERK pathway, modulating anti-inflammatory and immunomodulation activity, while Jinhuaqinggan granules targeted TNF, MAPK, and T-cell receptor signaling pathways, and Lianhuaqingwen a TCM formulation with broad-spectrum antiviral effect and effective to treat influenza virus's infection, also significantly inhibited the replication of SARS-CoV-2 with reduced pro-inflammatory cytokines production [43].

Drug repurposing

The fast-track approach used to widen the horizon of drug molecule by identifying new uses of FDA-approved drug candidates, which are yet not explored is termed as drug repurposing or drug repositioning techniques. Generally, it is recognized as the most influential technique over the traditional *de novo approach*, in which one has to need to identify potential leads and then synthesize them for their development as new drug candidates. Even in recent years, drugs such as quinidine, different kinase inhibitors, FDA-approved Niclosamide, and Azithromycin, etc. have been repurposed for the treatment of a different viral infection which includes dengue, Zika virus (ZIKV). In the current era of the COVID-19 pandemic, this technique is could be a powerful weapon for the fast-track drug discovery to end the pandemic. Research groups around the globe are exploring various FDA-approved drug molecules for the potential treatment of COVID-19. In this context, Ge., *et al.* has successfully used the drug repurposing technique to explore the potential of a poly-ADP-ribose polymerase 1 (PARP1) inhibitor named CVL218 against SARS-CoV-2 as a potential lead drug candidate. The finding by Ge and co-workers suggested that compound CVL218 was able to inhibit the replication of SARS-CoV-2 with an EC_{50} value of 5.12 μM. Moreover, CVL218 was found to exhibit an anti-inflammatory effect by reducing the CpG-induced IL-6 production by 50% and 72.65% in peripheral blood mononuclear cells at concentrations of 1 μM and 3 μM after 12 hours of treatment, respectively. Hence, it can be repurposed as a potential treatment of COVID-19 along with the reduction of cytokine storm to reducing SARV-CoV-2 induced inflammation. The spike protein of highly pathogenic human coronaviruses gains its entry into the host cells via serine protease primer i.e., transmembrane protease serine 2 (TMPRSS2). Blocking the activity TMPRSS2 could be a potential target for COVID-19 treatment. Camostat mesylate, originally developed in Japan in 1980, is a transmembrane protease serine 2 (TMPRSS2) inhibitor that has shown the ability to prevent the entry of the virus into Caco-2 ($TMPRSS2^+$) cells rather than 293T ($TMPRSS2^-$) and thus preventing the spread of infection as reported by Hoffmann., *et al*. Moreover, this molecule has a well-recognized safety profile and used for the treatment of inflammation induced by acute pancreatitis and hence can be explored in COVID-19 patients [44]. In nutshell, it can be concluded that drug repurposing can help the scientific community to identify potential treatments for COVID-19.

Recent progress in the development of new SARS-CoV inhibitors

Recently, Zhang., *et al.* designed and synthesized a new family of α-ketoamide inhibitors. They have found that compound 1 was the most potent against the SARS-CoV-2 with an IC_{50} value of 0.65 μM. Mechanistic studies established that compound 1 is an effective inhibitor of SARS-CoV-2 3CLpro [45]. The crystal structure of SARV-CoV-2 protein i.e. 3CLpro (PDB code: 6LU7) along with a peptidomimetic inhibitor named N3 has been established by Yang and co-worker. Virtual and high throughput screening was performed with various chemical libraries of approved drugs and identified various molecules either under clinical trials or approved drug candidates as potential 3CLpro inhibitors. Several potential compounds were identified whose IC_{50} values ranged between 0.67-21.4 μM. Among these compounds, some are FDA-approved drugs like disulfiram and carmofur while others like ebselen, shikonin, tideglusib, and PX-12 are currently under clinical development or preclinical studies. Further, Zhou., *et al*. reported series of compounds based upon vinyl sulfones (2 and 3) as promising protease inhibitors. These compounds inhibited SARS-CoV in low the nanomolar range with IC_{50} values 0.08 and 0.32 μM, respectively. Moreover, a combination of vinyl sulfone and camostat was found successful *in vivo* by notably increasing the survival meantime of mice compared to the control group (Figure 3).

Therapeutics agents against COVID-19 under various clinical phases are depicted in table 2.

Vaccine developmental status against COVID-19

Vaccination remains a critical tool to prevent further illness and death and to control the pandemic. It is one of the best and ideal tools for the treatment of COVID-19 thereby directing several efforts for its development. Various approaches like DNA, RNA, recombinant subunit, and mRNA are used by various researchers for

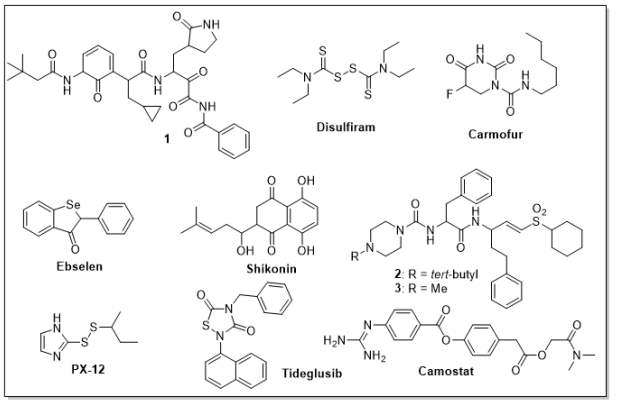

Figure 3: New small molecules as potential SARS-CoV-2 inhibitors.

the development of vaccines. The development of vaccines represents a more promising and long-term therapeutic strategy to prevent COVID-19 outbreaks. Multiple nucleic acid-based vaccines with the sequencing of the COVID-19 genome have been proposed and most of them are based on the S protein-coding sequence [46]. List of approved vaccines and those under clinical development are shown in table 3 and 4, while table 5 summarizes different categories or types vaccine candidates undergoing clinical trials.

Approaches and development of different vaccine candidates

Protein subunit vaccines

It is the one that is based on synthetic peptides or recombinant antigenic proteins. The subunit vaccine employs an adjuvant to potentiate the vaccine-induced immune response by increasing the biological half-life of the antigenic material. The S-protein comprises two subunits. The S1 subunit contains the NTD, RBD, and

S. No.	Medication class	Trade name (Generic name)	Developer	Trial phase
1.	Angiotensin-(1–7) peptide	TXA127	Constant Therapeutics	Phase 2
2.	Anthelmintic	Niclocide (niclosamide)	ANA Therapeutics	Phase 2/3
3.	Anti-TNF	Humira (adalimumab)	University of Oxford; Pharm-Olam	Phase 2/2
4.	Antibody cocktail	Casirivimab/imdevimab (REGN-COV2)	Regeneron	Phase 1/2/3
5.	Anticoagulant	Heparin (UF and LMW)	NHLBI	Phase 2/3/4
6.	Anticoagulant	Eliquis (Apixaban)	NHLBI	Phase 3
7.	Antigout agent	Colchicine (Mitigare, Colcrys)	NHLBI; Bill and Melinda Gates Foundation; Government of Quebec	Phase 2/3
8.	Antihelmintic	Ivermectin	Various	Phase 2/3
9.	Antirheumatic agent	Bucillamine	Revive Therapeutics Ltd.	Phase 3
10.	Antiviral	SNG001	Synairgen	Phase 2/3
11.	Antiviral	Molnupiravir (MK-4482)	DRIVE; Ridgeback Biotherapeutics; Merck	Phase 2
12.	Antiviral	Veklury (remdesivir)	Gilead Sciences	Phase 2/3
13.	Antiviral	Avigan (favilavir/avifavir)	Fujifilm Toyama Chemical (as Avigan); Zhejiang Hisun Pharmaceutical	Phase 2/3
14.	Antiviral	Galidesivir	BioCryst Pharmaceuticals	Phase 1b
15.	Antiviral	AT-527	Atea Pharmaceuticals, Inc.	Phase 2
16.	Autologous adipose-derived stem cells	AdMSCs	Celltex Therapeutics	Phase 2
17.	Biguanide	Metformin (Glucophage, Glumetza, Riomet)	University of Minnesota	Phase 2/3

18.	Dihydroorotate dehydrogenase (DHODH) inhibitor	PTC299	PTC	Phase 2/3
19.	Glucocorticoid	Dexamethasone (Dextenza, Ozurdex, others)	Various	Phase 2/3
20.	Glucocorticoid	Hydrocortisone	Various	Phase 3
21.	H2 blocker	Pepcid (famotidine)	Yamanouchi Pharmaceutical Co.; J&J; Merck	Phase 3
22.	HIV protease inhibitor	Kaletra (lopinavir-ritonavir)	AbbVie	Phase 2/4
23.	HIV-1 Rev protein inhibitor	ABX464	Abivax	Phase 2b/3
24.	Host defense protein (HDP) mimetic	Brilacidin (PMX-30063)	Innovation Pharmaceuticals	Phase 2
25.	IL-6 receptor agonist	Actemra (tocilizumab)	Roche	Phase 3
26.	IL-6 receptor agonist	Kevzara (sarilumab)	Sanofi; Regeneron	No longer being studied for COVID-19
27.	Immunoglobulin	Convalescent plasma	Various	Phase 1/2
28.	JAK inhibitor	Olumiant, Baricinix (baricitinib)	Eli Lilly	Phase 3/4
29.	Kinase inhibitor	Calquence (acalabrutinib)	AstraZeneca	Phase 2
30.	Mitogen-activated protein kinase (MAPK) inhibitor	Losmapimod	Fulcrum Therapeutics	Phase 3
31.	Monoclonal antibodies	Bamlanivimab + etesevimab	Lilly; Junshi Biosciences	Phase 2/3
32.	Monoclonal antibody	AZD7442	AstraZeneca; Vanderbilt University Medical Center	Phase 3
33.	Monoclonal antibody	Bamlanivimab (LY-CoV555)	Lilly; AbCellera	Phase 2/3
34.	Monoclonal antibody	Etesevimab (LY-CoV016, JS016)	Lilly; Junshi Biosciences	Phase 1
35.	Monoclonal antibody	VIR-7831/VIR-7832 (GSK4182136/ GSK4182137)	Vir Biotechnology, Inc.; GSK	Phase 1b/2a/2/3
36.	Monoclonal antibody	Ilaris (canakinumab)	Novartis	Phase 3
37.	Monoclonal antibody	Regkirona (CT-P59, regdanvimab)	Celltrion	Phase 3
38.	Monoclonal antibody	Ultomiris (ravulizumab)	Alexion	Phase 3
39.	Monoclonal antibody	BRII-196/BRII-198	Brii Biosciences Limited	Phase 3
40.	Monoclonal antibody	COVI-AMG/COVI-DROPS (STI-2020)	Sorrento Therapeutics	Phase 1
41.	Monoclonal antibody	Mavrilimumab	Kiniksa Pharmaceuticals	Phase 2
42.	Monoclonal antibody	PRO 140 (leronlimab)	CytoDyn	Phase 2b/3
43.	Monoclonal antibody	Lenzilumab	Humanigen; Catalent	Phase 3
44.	Monoclonal antibody	Remicade (infliximab)	Janssen	Phase 2/3
45.	Monoclonal antibody	COVI-GUARD (STI-1499)	Sorrento Therapeutics	Phase 1

46.	Monoclonal antibody	Takhzyro (lanadelumab)	Takeda (Shire)	Phase 1b
47.	Monoclonal antibody	Gimsilumab	Roivant Sciences	Phase 2
48.	Monoclonal antibody	Otilimab	MorphoSys; GSK	Phase 2
49.	Nitric oxide	INOpulse	Bellerophon Therapeutics	Phase 3
50.	Oral sodium-glucose co-transporter 2 (SGLT2) inhibitor	Farxiga (dapagliflozin)	Bristol-Myers Squibb	Phase 3
51.	PIKfyve inhibitor	LAM-002A (apilimod dimesylate)	AI Therapeutics, Inc.	Phase 2
52.	Recombinant fusion protein	MK-7110 (CD24Fc/SACCOVID)	OncoImmune; Merck	Phase 3
53.	Recombinant human plasma	Rhu-pGSN (gelsolin)	BioAegis Therapeutics	Phase 2
54.	rhACE2	APN01	Apeiron Biologics	Phase 2
55.	RIPK1 inhibitor	DNL758 (SAR443122)	Sanofi; Denali Therapeutics	Phase 1b
56.	Serine protease inhibitor	Foipan/Foistar (camostat mesilate)	Ono Pharmaceutical	Phase 2/3
57.	Small-molecule inhibitor	PF-00835321 (PF-07304814)	Pfizer	Phase 1b
58.	Small-molecule protein inhibitor	BLD-2660	Blade Therapeutics	Phase 2
59.	Synthetic human vasoactive intestinal peptide (VIP)	Zyesami (aviptadil, RLF-100)	NeuroRx; Relief Therapeutics	Phase 2/3
60.	Tyrosine kinase inhibitor	STI-5656 (abivertinib)	Sorrento Therapeutics	Phase 2
61.	VIP receptor agonist	PB1046	PhaseBio	Phase 2

Table 2: List of therapeutic candidates against COVID-19.

S. No.	Name	Vaccine type	Developers	Approved in countries for use
1.	Comirnaty (BNT162b2)	mRNA-based vaccine	Pfizer, BioNTech, Fosun Pharma	Australia, Canada, Colombia, Greenland, Iceland, Iraq, Israel, Jordan, Malaysia, Mexico, New Zealand, Norway, Oman, Panama, Philippines, Qatar, Saudi Arabia, Serbia, Singapore, Switzerland, UAE, UK, US, WHO
2.	Moderna COVID19 Vaccine (mRNA-1273)	mRNA-based vaccine	Moderna, BARDA, NIAID	Canada, EU, Faroe Islands, Greenland, Iceland, Israel, Norway, Qatar, Saudi Arabia, Singapore, Switzerland, United Kingdom, United States

3.	COVID-19 Vaccine AstraZeneca (AZD1222); also known as Covishield	Adenovirus vaccine	BARDA, OWS	Argentina, Bahrain, Bangladesh, Brazil, Chile, Dominican Republic, Ecuador, El Salvador, EU, Hungary, India, Iraq, Mexico, Morocco, Myanmar, Nepal, Pakistan, Philippines, Saudi Arabia, South Africa, South Korea, Sri Lanka, Thailand, UK, Vietnam
4.	Sputnik V	Non-replicating viral vector	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Algeria, Argentina, Armenia, Bahrain, Belarus, Bolivia, Guinea, Hungary, Iran, Kazakhstan, Laos, Lebanon, Mexico, Mongolia, Nicaragua, Pakistan, Palestine, Paraguay, Republika Srpska, Russia, Serbia, Tunisia, Turkmenistan, United Arab Emirates, Venezuela
5.	CoronaVac	Inactivated vaccine (formalin with alum adjuvant)	Sinovac	Azerbaijan, Bolivia, Brazil, China, Chile, Colombia, Indonesia, Laos, Turkey, Uruguay
6.	BBIBP-CorV	Inactivated vaccine	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	Bahrain, Cambodia, China, Egypt, Hungary, Jordan, Iraq, Laos, Macau, Morocco, Pakistan, Peru, Serbia, Seychelles, UAE
7.	EpiVacCorona	Peptide vaccine	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	Russia, Turkmenistan
8.	Convidicea (Ad5-nCoV)	Recombinant vaccine (adenovirus type 5 vector)	CanSino Biologics	Mexico, China (military use)
9.	Covaxin	Inactivated vaccine	Bharat Biotech, ICMR	India

Table 3: List of approved vaccines against COVID-19 in different countries.

S. No.	Candidate	Mechanism	Sponsor	Current Status	Institution
1.	JNJ-78436735 (formerly Ad26. COV2.S)	Non-replicating viral vector	Johnson and Johnson	Phase 3	Johnson & Johnson
2.	NVX-CoV2373	Nanoparticle vaccine	Novavax	Phase 3	Novavax
3.	ZF2001	Recombinant vaccine	Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences	Phase 3	Various
4.	CVnCoV	mRNA-based vaccine	CureVac; GSK	Phase 2b/3	CureVac

5.	Bacillus Calmette-Guerin (BCG) vaccine	Live-attenuated vaccine	University of Melbourne and Murdoch Children's Research Institute; Radboud University Medical Center; Faustman Lab at Massachusetts General Hospital	Phase 2/3	University of Melbourne and Murdoch Children's Research Institute; Radboud University Medical Center; Faustman Lab at Massachusetts General Hospital
6.	INO-4800	DNA vaccine (plasmid)	Inovio Pharmaceuticals	Phase 2/3	Center for Pharmaceutical Research, Kansas City. Mo.; University of Pennsylvania, Philadelphia
7.	VIR-7831	Plant-based adjuvant vaccine	Medicago; GSK; Dynavax	Phase 2/3	Medicago
8.	UB-612	Multitope peptide-based vaccine	COVAXX	Phase 2/3	United Biomedical Inc. (UBI)
9.	ZyCoV-D	DNA vaccine (plasmid)	Zydus Cadila	Phase 2	Zydus Cadila
10.	Abdala (CIGB 66)	Protein subunit vaccine	Finlay Institute of Vaccines	Phase 2	Finlay Institute of Vaccines
11.	BNT162	mRNA-based vaccine	Pfizer, BioNTech	Phase 1/2/3	Multiple study sites in Europe, North America, and China
12.	AdCLD-CoV19	Adenovirus-based vaccine	Cellid; LG Chem	Phase 1/2a	Korea University Guro Hospital
13.	Nanocovax	Recombinant vaccine (Spike protein)	Nanogen Biopharmaceutical	Phase 1/2	Military Medical Academy (Vietnam)
14.	EuCorVac-19	nanoparticle vaccine	EuBiologics	Phase 1/2	Eunpyeong St. Mary's Hospital
15.	Mambisa (CIGB 669)	Protein subunit vaccine	Finlay Institute of Vaccines	Phase 1/2	Finlay Institute of Vaccines

Table 4: List of vaccine candidates under clinical development against COVID-19.

S. No.	Abbreviations	Type of vaccine	Number of vaccines
1.	PS	Protein subunit	22
2.	VVnr	Viral Vector (non-replicating)	10
3.	DNA	DNA	8
4.	IV	Inactivated Virus	10
5.	RNA	RNA	7
6.	VVr	Viral Vector (replicating)	3
7.	VLP	Virus-Like Particle	2
8.	VVr + APC	VVr + Antigen Presenting Cell	2
9.	LAV	Live Attenuated Virus	1
10.	VVnr + APC	VVnr + Antigen Presenting Cell	1
		Total	66

Table 5: Vaccine category and number of candidates under clinical development.

RBM domains while the S2 subunit includes FP, HR 1, &2. The viral entry is mediated through endocytosis by utilizing the S-protein mediated binding to the hACE2 receptor. Therefore, the S-protein and its antigenic fragments act as the crucial targets for the subunit vaccine. The S-glycoprotein is a dynamic protein that possesses two conformational states i.e., pre-fusion and post-fusion state. Therefore, the antigen must maintain its integrity, surface chemistry, and profile of the original pre-fusion spike protein to preserve the epitopes for inducing optimum antibody responses. Moreover, the means to target the masked RBM as an antigen will enhance the neutralizing antibody response and improve the overall efficacy of the vaccine. Numerous vaccine candidates are under pre-clinical and clinical trials among which Abdala (CIGB 66) is presently in phase II sponsored by the Finlay Institute of Vaccines [46].

Nanoparticle-based vaccines

Nanoplatforms or Nanoparticle-based vaccines represent a progressive and effective approach in controlling and eliminating the widespread of this pandemic. Various nano-materials either synthetic or natural finds application in the ongoing therapeutic and prophylactic strategies to counter this threat. These nanocarriers can be widely categorized in organic and inorganic polymeric materials, Virus-like proteins (VLPs), etc. are available as antigen carriers. Nanoparticles can be conjugated with mimic viruses, antigenic epitopes and thus it can provoke antigen-specific lymphocyte proliferation as well as cytokine production through encapsulation or covalent functionalization. In addition to this, it is also determined that mucosal vaccination through an intranasal or oral spray can not only stimulate immune reactions at the mucosal surface but also provoke systemic responses. NVX-CoV2373, a nanoparticle-based vaccine derived from coronavirus S-protein is in phase 3 of clinical trials sponsored by Novavax, Inc. The protein is stably expressed in the baculovirus system and the company planned to utilize the matrix-M adjuvant to enhance the immune response against SARS-CoV2 protein by the introduction of high levels of neutralizing antibodies [47].

Pathogen-specific artificial antigen-presenting cells

It is very well known that antigen-specific T-cells can exterminate cancer cells as well as viral infections. Thus, producing a large amount of T cells with viral antigen specificity in a timely manner may well help us endure the invasion of COVID-19. The T-cell can be yielded in massive amounts by use of suitable antigen-presenting cells that can trigger effector T cells which can further promote the differentiation and proliferation of the corresponding effector i.e., cytotoxic T-cells. Clinical trials for the evaluation of safety and immunogenicity of artificial antigen-presenting cells alone as well as in combination with antigen-specific cytotoxic T-cells have been initiated in the current era of the pandemic (NCT04299724, NCT04276896).

mRNA vaccine

mRNA vaccines belonging to a class that represents a promising alternative to conventional vaccine approaches due to their high potency, capacity for rapid development, and potential for low-cost manufacture, and safe administration with almost no potential risk of insertional mutagenesis. The use of mRNA has several advantages over subunit, killed, and live attenuated virus, as well as DNA-based vaccines. First includes safety as mRNA is a non-infectious and non-integrating platform. Moreover, mRNA is degraded by normal cellular processes and it's *in vivo* half-life can be modulated through various modifications and delivery methods. Second is the efficacy as various modifications make mRNA more stable and highly translatable. mRNA is the minimal genetic vector therefore anti-vector immunity is avoided thus mRNA vaccines can be administered repeatedly. The third merit is the production as mRNA vaccines have the potential for rapid, inexpensive, and scalable manufacturing owing to the high yields of *in vitro* transcriptional processes. Thus, suggesting the potential of mRNA vaccines as a therapeutic strategy for viral conditions. Among this category antigen-encoding nucleoside modified mRNA encapsulated into lipid nanoparticles (mRNA-LNP) has been the most widely explored. Nucleoside-modified mRNA-LNP vaccines have promoted protective immune responses against a variety of pathogens. These mRNA-LNP vaccines encode for full-length SARS-CoV-2 spike protein which induced strong type I $CD4^+$ and $CD8^+$ T cell responses, as well as long-lived plasma and memory B cell responses. Recently two vaccines, Comirnaty (BNT162b2) and Moderna COVID-19 Vaccine (mRNA-1273) have been approved under this category while several candidates are in the preclinical and clinical phases [48].

DNA vaccines

DNA vaccine utilizes a gene from a virus or bacteria to stimulate the immune system. When the DNA vaccine is administered to a patient, the machinery in their cells makes a viral or bacterial protein recognized as a foreign body by their immune system. Like any vac-

cine, the immune system will then recognize the bacteria or virus in the future preventing the incidence of disease. Conventional vaccines differed from DNA vaccines as they are made of whole bacteria or viruses (either inactivated or dead) or a part of the bacteria or virus, such as a protein. DNA vaccine includes delivering genes or fragments of it, encoding immunogenic antigens to the host's cells by employing DNA plasmids as a vector. This approach induces both humoral and cell-mediated immune responses efficiently. The genetic material is introduced directly in the host's cell nucleus. Once it reaches there, the mammalian promoter present in the vector structure activated, triggering the transcription of the gene used for the vaccine utilizing the host's cellular machinery. The antigen-presenting cells (APCs) are the major target cells to receive the genetic material. Cells other than APC, such as the myocytes, use MHC-I for the antigen presentation, and APC, such as dendritic cells (DCs), can use MHC-II, resulting in cross-priming and presentation of antigens to both CD4+ and CD8+ T-cells. Currently, several vaccine candidates are under the clinical pipelines under this category including INO-4800, sponsored by Inovio Pharmaceuticals which is under Phase 3, and ZyCoV-D by Zydus Cadila that is phase 2 of clinical trials [49,50].

Viral-vectored vaccines

Viral vectored vaccines are live viruses that are genetically engineered to express one or more heterologous antigens. There are two types of viral vector vaccines: replicating viral vector vaccines or non-replicating viral vector vaccines. The vaccines for COVID-19 are non-replicating which require higher doses but are safer than replicating viral vectors. These vaccines are highly specific in delivering the genes to the target cells, resulting in efficient gene transduction thus inducing an optimum immune response. They offer a long term and high level of antigenic protein expression and therefore, have a great potential for prophylactic use as these vaccines trigger and prime the cytotoxic T cells (CTL) which ultimately leads to the elimination of the virus-infected cells [49].

Recently, COVID-19 Vaccine AstraZeneca (AZD1222); also known as Covishield which is an adenovirus-based vaccine has been in the last stage of clinical phase. The Global Advisory Committee on Vaccine Safety COVID-19 subcommittee (GACVS) hold a virtual meeting on 16 and 19 March, 2021 to review the available data on thromboembolic events (blood clots) and thrombocytopenia (low platelets) after vaccination with the AstraZeneca COVID-19 vaccine. After the meeting, the subcommittee came to the conclusions stating that vaccine displayed positive benefit-risk profile, with tremendous potential to prevent infections and reduce deaths across the world. The available data do not suggest any overall increase in clotting conditions such as deep venous thrombosis or pulmonary embolism following administration of COVID-19 vaccines. Another vaccine, Sputnik V developed by Gamaleya Research Institute, Acellena Contract Drug Research, and Development, Russia has also been approved. Convidicea (Ad5-nCoV), recombinant vaccine (adenovirus type 5 vector) sponsored by CanSino Biologics has also been approved. While several candidates are currently under development phases including Shenzhen Geno-Immune Medical Institute-sponsored LV-SMENP DC presently in phase I/II [49].

Inactivated vaccine

Purified inactivated viruses have been traditionally used for vaccine development and be effective in preventing various viral diseases, such as influenza. The inactivated SARS-CoV-2 vaccine candidate, BBIBP-CorV, displayed potency and safety in animal models thus getting approved clinical trials. The inactivated SARS-CoV-2 vaccine containing aluminum hydroxide developed by Sinovac has entered phase 3 clinical trials, with results from the phase 2 trial demonstrating that two doses of 6 μg/0.5mL or 3 μg/0.5mL of the vaccine were well-tolerated and immunogenic in healthy adults. Another recently approved vaccine is Covaxin developed by Bharat Biotech, India that has shown tremendous results in the clinical phases [49].

Future Perspective and Conclusion

SARS-CoV-2 is the third pandemic situation originated from the jump of coronaviruses from animals to human. Since its first outbreak in December 2019 in Wuhan, China, it is proving fatal to the human race affecting 15.5 Cr individuals and has registered 3.24 million deaths worldwide as per 6 May, 2021. As the disease progresses many challenges are likely to develop, especially in critically ill patients such as the involvement of multiple organs and acute respiratory distress syndrome. The virus is mutating and multiple variants of the virus that causes COVID-19 have been reported globally, which further worsen the situation. Remdesivir has proven to be effective against SARS-CoV-2, but still, supportive care, isolation and combination therapy is required to treat severely ill patients. This article provides a summary of the current state of understanding of the COVID-19 pandemic. The structural

features of COVID-19, outbreaks, diagnostics, and various possible therapeutic approaches for disease control under investigation have been addressed. Development status of various RNA and DNA-based vaccines, various antibodies, protease inhibitors, heterocyclic-based antiviral drug discovery including repurposing of different drugs have been initiated for the treatment of COVID-19, but these approaches are long-term as they require rigorous safety testing. The recurrence of existing therapeutic agents yet intended for other virus infections and pathologies appears to be the only realistic solution as a rapid response measure to an emerging pandemic since most of these agents have already been tested for protection. We assume that the current pandemic emergency would cause more systemic drug repurposing approaches focused on a comprehensive data analysis. Computational techniques summed up with the continuation of experimental studies aimed at testing computationally predicted antiviral agents can lead to the production of potential anti-CoV agents. Different countries such as India, USA, UK, Russia etc. have initiated their country wide immunization to combat the current pandemic situation but it is more likely that in the long term treatment with more than one vaccine will be needed to ensure the protection and immunity against the different variants of the virus. We are speculating that promoting progress in decoding SARS-CoV-2 will lead to the development of successful broad-spectrum anti-SARS-CoV-2 drugs and effective vaccines in the near future.

Conflict of Interest

The author declares no conflict of interests.

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Volume 5 Issue 7 July 2021