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Chapter

Different Therapeutic Strategies to Tackle the Infection Associated with COVID-19

Meemansha Sharma, Thakur Uttam Singh, Madhu Cholenahalli Lingaraju and Subhashree Parida

Abstract

Covid-19 is a pandemic and the whole world is facing the loss in terms of morbidity and mortality of the human resources. Therefore, there is an urgent need for various therapeutic agents or drugs to treat the covid-19 patients. Although, vaccination process is under way, it is not possible to provide the vaccination to whole world in a short period. Therefore, it is an essential strategy to work on the various therapeutic aspects of covid-19 treatment. The present book chapter will discuss and review the various aspects of the treatment strategies of the covid-19. Further, we will provide an overview of the virus and host based potential therapeutic targets along with existing therapeutics which are effective against SARS-CoV-2 virus. Also, the novel vaccines are being developed against covid-19 deadly virus will be discussed.

Keywords: SARS-CoV-2, covid-19, therapeutics, pandemic

1. Introduction

The new covid-19 pandemic was reported in Wuhan, China in December, 2019 [1]. This disease is caused by corona virus also known as SARS-CoV-2 and characterized by severe acute respiratory distress syndrome [2]. As per the recent report of WHO on 20 December, 2020, there have been over 75 million cases and 1.6 million deaths reported worldwide since the start of the pandemic [3]. In 2002, SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) outbreak was reported in China then spread worldwide, whereas, MERS-CoV (Middle East Respiratory Syndrome Coronavirus) emerged in Saudi Arabia in 2012 with 37% mortality rate. Similar to SARS and MERS, newly identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to beta-coronaviridae family and showed close resemblance with them [4]. These three zoonotic viruses have pandemic potential and able to produce severe respiratory infection in humans [5].

The SARS-CoV-2 infection is transmitted through respiratory secretions either in droplet or aerosol form from one person to another [6]. Apart from respiratory secretions, urine, stool and close proximity with patients may be the sources for dissemination of SARS-CoV-2 [7, 8]. Based on phylogenetic studies, the genomic sequence of SARS-CoV-2 virus is 96% similar to bat corona viruses so these bats may be potential reservoir host for human corona virus [9]. However, there are

no clear evidences which have suggested virus transmission directly from bats to human population [10]. Further, some studies suggested that pangolins can be considered as intermediate hosts between bats and human [11, 12]. Severe infectious covid-19 cases have rapidly progressed to dyspnoea, shock and acute respiratory distress [13]. In addition, the other organ dysfunctions have also been reported from patients including severe cardiac injury, acute renal, gastrointestinal, liver injury, neurological defect along with coagulation impairment and death [13].

It is important to understand the virus biology, and replication cycle to identify effective therapies against SARS-CoV-2, because most of therapies are directly targeting the stages in the virus life cycle. Highly pathogenic SARS-CoV-2 are enveloped, single-stranded positive sense RNA betacoronavirus with size ranging from 80–120 nm, and their genomes encode non-structural proteins (nsps), structural proteins, and several accessory proteins [14]. Genome of RNA virus contains ten open reading frames (ORF1–10) and has total 29,903 nucleotides [15]. Among the ten ORFs ORF2–10 generates four structural proteins S (spike), N (nucleocapsid), E (Envelop protein), M (Membrane protein) along with auxillary proteins. However, large replicase polyproteins (PP1a/b) encoded by ORF1ab further gets cleaved by proteolytic enzymes into non structural proteins (nsp1–16) [15].

The SARS-CoV-2 virus entry in host cell is mediated with attachment of the spike (S) glycoprotein with the host angiotensin-converting enzyme 2 (ACE2) receptor thereby infection process starts [16]. Further, virus S protein cleaved by the cathepsin L proteases which get activated in a pH- dependant manner allows the release of viral genome into host cell cytoplasm [17]. In addition, other host cell proteases like TMPRSS2 (Transmembrane Protease Serine Type-2) and TMPRSS11D (Airway trypsin like protease) participate in the cleavage of spike protein into its constituents (S1 and S2) which further lead to entry of virus genome into host cell through non endocytic pathway [18]. S1 subunit of spike protein possesses receptor binding domain (RBD) which binds with host receptors and S2 subunit favors fusion of viral membrane with host cell [19]. Once the virus genome released inside the host cell, then host ribosomes are involved in the process of translation of virus genome containing ORF1ab into replicase polyproteins PP1ab [20]. These PP1ab further cleaved by important viral proteases include 3CLpro (3 chymotrypsin like proteases) and PLpro (papain like proteases) to generate nsp2–16 [20]. These nsp2–16 are participated in virus replication and transcription complex, while virus structural proteins are translated from another ORF2–10 containing viral genome and contribute to outer structure of virus [21]. At last, the newly born virions are delivered outside the infected cell by exocytosis after completion of their structural assembling in the endoplasmic reticulum golgi bodies complex [22].

The WHO (world health organization) has declared covid-19 a public health emergency due to its high spreading potential across the world. Although, vaccine development trial has almost finished and vaccination drive is going to be started. However, till now there are no effective therapies or specific drug candidates against this communicable disease. Thus, it is required to understand detail biology of virus (SARS-CoV-2) to further elucidate novel drug therapeutics.

2. Therapeutic agents to tackle the covid-19 infection

2.1 ACE-2 modulators

Like SARS-CoV, it is confirmed that SARS-CoV-2 virus also interacts with ACE-2 human enzyme for entry and replication into the host cell. SARS-CoV-2 spike protein has high binding affinity with ACE-2 enzyme present in respiratory epithelial

cell of host [23]. Hence, the therapeutics which inhibit spike protein-ACE-2 interaction would be considered effective therapy against SARS-CoV-2. ACE-2 enzyme is a zinc metalloproteinase which contains two domains in its structure which include amino terminal domain and carboxy terminal domain [5]. ACE-2 enzymes are exhibits in type-I and type-II alveolar cells of respiratory tract, liver, kidney, testes, heart and intestine [24]. Wu et al. [25] have found that ACE-2 enzymes are highly expressed in alveolar epithelial type-II cells in an around 83% which indicate these cell can be served as reservoir for virus. ACE-2 enzyme is a key regulator protein of RAS (Renin-Angiotensin System) system which contributes to vascular homeostasis [26]. In RAS system, angiotensinogen glycoprotein is cleaved by renin enzyme present in kidney to angiotensin-I, which has converted into angiotensin-II (Ang-II) by ACE-1. Further, Ang-II binds to angiotensin receptor (ATR1) and produces vasoconstriction, cell proliferation, inflammation, thrombosis and vascular constriction [27]. For the counterbalance of AngII- ATR_1 axis effect, AngII is cleaved by ACE-2 enzymes into Ang1–7 peptides [28]. These angiotensin peptides further act on MASR (mitochondrial assembly receptor) and exhibits protective effects such as anti-inflammatory, anti-apoptotic and vasodilatation. Rothlin and co-worker [29] have reported the protective effects of ACE inhibitors and angiotensin receptor blockers (ARBs). They have found that patients with Covid-19 infection are taking ACE inhibitors and angiotensin receptor blockers exhibited lower mortality as compared with non-user patients. Previous study revealed that SARS-CoV virus down-regulates the ACE-2 enzymes present in host cell surface and increased ACE enzyme activity which lead to severe lung injury [30]. Increased ACE enzyme activity has been observed in SARS-CoV-2 patients. Hence, it has been proposed that delivery of soluble ACE-2 recombinant protein compete with host ACE-2 enzymes for the SARS-CoV-2 spike protein and ultimately neutralize the virus load and further, protect the patients from lung injury. For this purpose, recombinant human ACE-2 such as APN01 and GK2586881 have been analyzed and found effective in patient suffered from acute severe respiratory syndrome (**Figure 1**) [31].

2.2 TMPRSS2 inhibitors

Transmembrane serine protease-2 (TMPRSS-2) is present in host epithelium cells of various tissues [32]. It is involved in the pathogenesis of SARS-CoV-2 through cleavage of spike protein and facilitates virus entry into host cell [33]. Matsuyama et al. [34] demonstrated that over-expressed protein TMPRSS-2 containing vero E6 cell lines are susceptible for SARS-CoV virus infection and used as pharmacological tool for SARS-CoV-2 research. Thus any drug candidate which inhibits TMPRSS-2 protease may be effective in SARS-CoV-2 infection. In this regard, *in vitro* study conducted against SARS-CoV-2 to check the efficacy of compound camostat mesylate blocked the spike mediated virus entry in caco-2 cells [35]. In addition, some repurposing studies have been conducted to evaluate the efficacy of other proteases inhibitors such as nafamostat, 4-(2 aminomethyl) benzenesulfonyl fluoride and mucolytic drug bromhexine which can offer new therapeutic option for this pandemic (**Figure 1**) [36, 37].

2.3 JAK–STAT inhibitors

In covid-19 infection, patients suffer from severe acute respiratory syndrome in which huge amounts of various cytokines are released from immune cells leading to multiorgan failure and death [38]. Moreover, JAK–STAT signaling pathway is involved in SARS-CoV-2 virus entry into host cell which has linked with AAK1 (Adaptor-associated protein kinase-1) related clathrin mediated endocytosis [39].

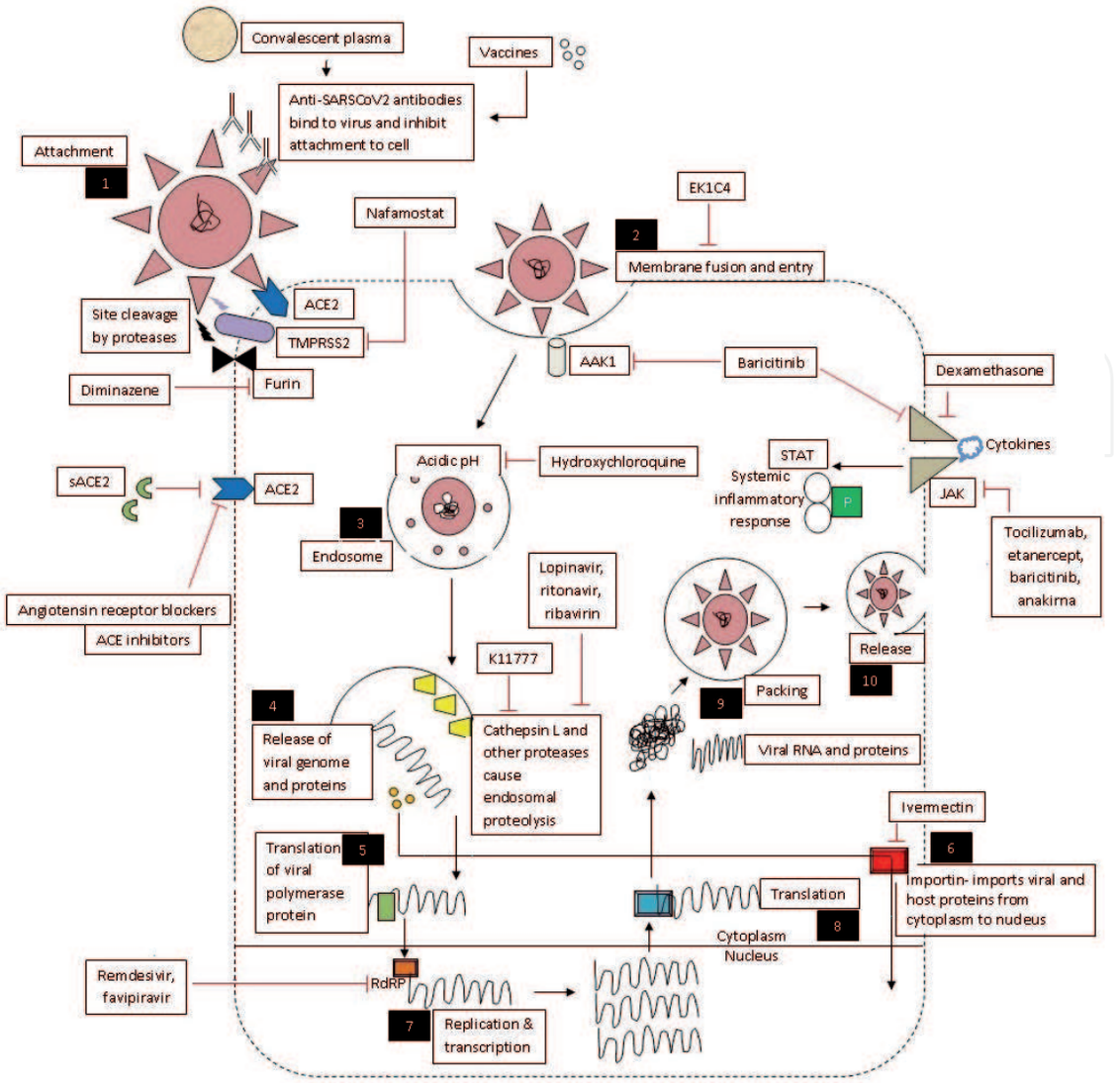


Figure 1.
Diagram showing the therapeutics approach to treat the infection of covid-19 patients.

Activation of JAK–STAT pathway through Ang-II/AT_1R may generate cytokines storm including IL-1, IL-2, IL-6, IL-7, IL-10 and TNF-α [39]. Thus, it may be suggested that JAK–STAT inhibitors could be potential therapeutics for the covid-19 infection. Further, Junior and co-workers [40] have shown that baricitinib, a JAK–STAT inhibitor, has potential to prevent generation of cytokines through inhibition of JAK–STAT signaling and also block the entry of SARS-CoV-2 via inhibiting AAK1 related clathrin mediated endocytosis (**Figure 1**).

2.4 Cathepsin L inhibitors

Cathepsin L is a cysteine protease reside in endosomes and works in acidic pH [41]. It cleaves S1 virus spike glycoprotein and facilitates three actions including virus entry into host cell, virus-host cell endosomal membrane fusion and RNA release. Serine protease (TMPRSS-2) acts on the surface of host cell membrane in neutral pH [42], whereas, cathepsin L mediates its action at host cell membrane as well as inside the endosomes in acidic pH [43]. Therefore, Liu and coworkers, [17] have proposed that the combined use of serine protease and cathepsin-L inhibitors could be effective therapeutics to prevent virus entry and their genome release inside the host cell thereby inhibit the virus replication. In addition, they have also mentioned some cathepsin-L

inhibitors compounds which are found effective against coronavirus infection such as dec-RVKR-CMK, K11777, small molecule 5705213, MDL28170, SSAA09E1, EST, and oxocarbazate. Based on the proposed mechanism, it is reported that the combined use of TMPRSS-2 inhibitors including camostat and nafamostat mesylate along with cathepsin-L inhibitor E64d have shown inhibitory potential against SARS-CoV and SARS-CoV-2 infection in human epithelial cells (**Figure 1**) [44].

2.5 Furin inhibitors

Furin, is a human protease enzyme, present in multiple tissues and highly expressed in lungs [45]. It has been reported that SARS-CoV-2 virus contains furin like cleavage site (FCS) in its spike protein which has made covid-19 virus more pathogenic in nature as compared to other ancestors virus of coronaviridae family [46]. SARS-CoV-2 virus utilizes host furin protease for the cleavage of spike protein and gain entry into the host cell. Moreover, mortalities from SARS-CoV-2 infection have been reported in those patients compromised with cardiac disease, diabetes, obesity and hypertension and likely to be associated with higher circulating furin level [47]. Hence, scientists have drawn attention towards furin inhibitors to provide new therapeutic intervention against covid-19 infection (**Figure 1**).

2.6 Inhibitors of virus structural proteins and enzymes

Structural proteins and virus encoded enzymes of SARS-CoV-2 may be considered as important drug targets because these are responsible for virus survival and propagation. Researchers and pharmaceuticals companies have focused to develop short interfering RNA (siRNA) based therapeutics to target virus structural proteins and enzymes such as 3CL pro, PLpro and RNA dependant RNA polymerases to combat covid-19 infection [48]. Some previous studies revealed that siRNA therapeutics have already been designed against SARS-CoV and MERS viruses and found effective in outbreaks [49]. In addition, heptad repeat 1 region (HR1) present in the S protein involved in fusion and entry of virus could also be a good target for the development of fusion inhibitors against covid-19 [50]. Xia and co-workers, [51] have developed EK1C4 fusion inhibitors which target SARS-CoV-2 spike protein and found effective in HCoV-OC43 challenged mice. Recently in clinical trials, many chemical peptides, existing drugs and new drug candidates have been recognized through virtual and high throughput screening techniques against SARS-CoV-2 coded enzyme proteases [52]. Based on computational strategy, 6LU7PDB compound has been identified which acts as non-covalent inhibitor of 3CL pro enzyme in SARS-CoV-2 infection [53]. Some 3CL pro enzyme inhibitors antiviral drugs such as lopinavir and ritonavir have been found effective against SARS-CoV-2 virus infection [54]. In addition, some therapeutics are also identified which showed high binding affinity with SARS-CoV PLpro enzyme such as ribavirin, valganciclovir, beta-thymidine and some natural products like platycodin D, baicalin and catechin [55]. Moreover, RNA dependant RNA polymerase (RdRp) inhibitor antiviral drug remdesivir was approved by FDA for emergency treatment for covid-19 patients [56]. However, still its role is controversial for the treatment of covid-19 patients (**Figure 1**).

2.7 Inhibitors of cytokines

During covid-19 infection, higher amounts of cytokines have secreted from inflammatory cells and serve as potential therapeutic targets for drug development.

The major cytokines, IL-6, IL-1, TNF and interferons are generated during cytokine storm which cause the increased vascular permeability, vascular leakage along with dissemination of virus which may lead to fatal pneumonia and acute respiratory distress syndrome [57, 58]. However, many neutralizing strategy against these inflammatory mediators are being used to cope with this cytokine storm in covid-19 pandemic. Chi and co-workers, [59] reported the use of antibodies against IL-6 receptor (tocilizumab and sarilumab) for the treatment of covid-19 infection. Anti-TNF drug etanercept has shown favorable effect in covid-19 patients [60]. Moreover, another targeting approach against cytokine IL-1 is important because it is the major cytokine present in higher amount in alveolar lavage of covid-19 patients and secreted from inflammatory macrophages and monocytes [61]. Cavalli & coworkers, [62] have reported the use of anakirna in high dose and found safe in 72% patients suffered from covid-19 and ARDS with non-invasive ventilation outside the ICU. Furthermore, interferons (IFNs) have immunostimulant and antiviral effects and their use as a treatment along with some antiviral drugs have been found effective against MERS, SARS and IBV viruses (**Figure 1**) [63].

2.8 Antiviral drugs

As per the previous information related with SARS & MERS outbreak, many existing anti-viral drugs are being repurposed against SARS-CoV-2 virus in covid-19 pandemic. Remdesivir is a prodrug that converts into active metabolite and inhibits RNA dependant RNA polymerases (RdRp) thereby preventing the viral RNA synthesis [64]. It is prescribed against ebola virus infection and reported to have *in vitro* antiviral activity towards SARS and MERS coronaviruses [56]. Recently, it was reported that remdesivir prevents SARS-CoV-2 infection in human liver cancer cells [65]. Based on one clinical trial, remdesivir has been found clinically effective in 36 out of 53 patients suffered from covid-19 infection and receiving oxygen support [66]. In addition, many clinical trials are being carried out to check efficacy of remdesivir in covid-19 patients in various countries. Hung & co-workers, [67] have conducted clinical trial by using the combination of triple antiviral drug include lopinavir, ritonavir and ribavirin along with interferon which were found more promising compared to antiviral drug used alone in patient suffered from covid-19 infection. Another antiviral drug, favipiravir inhibits viral RNA polymerase enzyme and reported to have antiviral activity against many RNA viruses such as influenza, bunya and filoviruses [68]. However, to check the clinical efficacy of favipiravir in covid-19 patients various clinical trials have been performed in China and found favorable results (**Figure 1**) [13].

2.9 Corticosteroids

Corticosteroids are extensively used for SARS-CoV, MERS-CoV, H1N1 influenza, and ARDS that have similar pathological features with covid-19. But, their role in reducing mortality and improving these conditions remain controversial [69]. It was reported that corticosteroids did not improve the outcome during the SARS and MERS outbreaks, but delayed viral clearance and increased rates of secondary infections [70]. A systemic review and meta-analysis are conducted in covid-19 patients by van-Paassen et al. [71], their findings based on observational and clinical studies suggested the beneficial effects of corticosteroids on mortality rate and reduced ventilation support. However, delayed viral clearance and increased secondary infection have also been observed. Similarly, the study has been conducted in China in 201 patients confirmed with covid-19 pneumonia. In 62 patients who received methylprednisolone likely had decrease risk of death [72]. As per

another report of Mishra & Mulani, [73] corticosteroids are not recommended in the late course of acute respiratory distress syndrome (ARDS) condition because their persistent use more than 2 weeks has increased risk of death in ARDS patients. It seems that corticosteroid treatment work like double edged sword in covid-19 fight, therefore duration of corticosteroid therapy needs to be clarified in clinical trials (**Figure 1**).

2.10 Convalescent plasma therapy

Convalescent plasma is obtained from donors who have recovered from covid-19 infection, possess antibodies against SARS-CoV-2 that may neutralize the virus and modify the immune response [74]. Convalescent plasma therapy offers short term protection strategy and generates immediate immune response in susceptible patients. This approach has already been used in earlier outbreak of corona viruses such as SARS and MERS [75]. In this corona pandemic, many clinical trials have also been conducted against SARS-CoV-2. Recently the clinical study conducted by Duan et al. [76] revealed that the convalescent plasma therapy was well tolerated and positively improved the clinical outcomes in severe covid-19 patients. Salazar et al. [77] reported the use of convalescent plasma therapy in 25 patients who had severe covid-19 disease and evaluated safety along with clinical outcomes at 14 day after the transfusion. They found clinical improvement in nine patients within seven days and other were discharged at day 14. Hence, convalescent plasma therapy has potential to treat covid-19 cases but some adverse events have also been reported such as allergic reaction, dyspnoea and acute lung injury [78] (**Figure 1**).

2.11 Ivermectin

Ivermectin is an broad spectrum antiparasitic drug and its antiviral activity has also been reported against number of viruses both *in vitro* and *in vivo* [79]. Recently, *in vitro* study revealed that ivermectin can inhibit SARS-CoV-2 replication by reducing viral RNA up to 5000 fold at 48 h. in culture cells [80]. However, the mechanism of action of ivermectin is not clearly known. Choudhry and Sharma, [81] have mentioned that ivermectin may act by creating acidic environment and blocking the importin IMP2/β1 mediated viral intranuclear import (**Figure 1**).

2.12 Hydroxychloroquine

Hydroxychloroquine has been prescribed since decades in the prevention and treatment of malaria as well as rheumatoid arthritis and systemic lupus erythematosus (SLE) like chronic inflammatory condition [82]. In SARS-CoV-2 pandemic, it was suggested that hydroxychloroquine may have potential to treat covid-19 affected patients [83]. Food and Drug Administration (FDA) has granted permission for emergency use of hydroxychloquine in the treatment of covid-19 patients during initial stage of pandemic [84]. Recently, many *in vitro* studies have been conducted and found that hydroxychloroquine possess inhibitory activity against SARS-CoV-2 [85, 86]. Further, several studies have been published regarding the use of hydroxychloroquine in covid-19 but results are conflicting. One population based cohort study conducted by Rentsch and coworkers, [87] stated that there was no difference observed in mortality of covid-19 patients who had already received hydroxychloroquine for the treatment of rheumatoid arthritis or systemic lupus erythematosus. Similarly, in an observational study in covid-19 hospitalized patients, hydroxychloroquine did not show any benefit over mortality reduction (**Figure 1**) [88].

2.13 Vaccines

Various vaccine developments are being carried out across the world due to urgent need to overcome this covid-19 pandemic. Now in covid-19 emergency, vaccines could only be considered as potent therapeutics against SARS-CoV-2 deadly virus which normalize social life and working environment as it was earlier before pandemic. For the effective vaccines development against SARS-CoV-2 virus, various components are being used which include inactive or live-attenuated viruses, virus-like particles, viral vectors, protein-based, DNA-based, and mRNA-based vaccines [89]. Till now various potential vaccine candidates have already been

Type/ plateform	Vaccine Construct	Developer	Clinical Stage & Current Status	References
Inactivated virus	Nucleic acid	National institute for communicable disease control and prevention, China	Phase-III	[91]
Inactivated virus	Novel corona virus inactivated vero cells	Bejing institute of biological products Sinopharma	Ongoing Phase-III	[92]
Inactivated virus	Whole virion inactivated SARS-CoV-2 antigen	Bharat Biotech, India	Phase-I / II (DCGI-CDSCO Approved for emergency use in India)	[93, 94]
DNA	S Protein	INOVIO Pharmaceuticals, with, International Vaccine Institute and Seoul National University Hospital of South Korea	Phase-I/ II (Phase–III study put on hold by FDA,US)	[95, 96]
RNA	LNP-encapsulated m-RNA	Moderna with national institute of allergy and infectious disease, USA	Phase-III [FDA issued Emergency Use Authorization (EUA)]	[97, 98]
RNA	Lipid nanoparticle encapsulated mRNA (BNT162b2)	BioNTech and Pfizer	Phase-III (FDA issued EUA)	[99]
Protein subunit	Full length SARS-CoV-2 glycoprotein nanoparticle vaccine	Novavax, USA	Phase-III (Planning to apply FDA EUA in April, 2021)	[100, 101]
Non replicating virus vector	ChAdOx1-S	University of Oxford with Astrazeneca (UK) and Serum Institute, India	Phase-III (Approved for emergency use in some selected countries)	[102, 103]
Non replicating virus vector	Adeno virus based	Gamaleya Research Institute (Sputnik U)	Phase-III (Approved for use in Russia)	[104]

Table 1.
List of various important vaccines which are developed or being in different development phases against covid-19 infection.

developed and undergone for vaccination shot which have completed their clinical evaluation phase successfully [90]. However, several new vaccines are still under clinical developmental phase (**Figure 1**). Some important vaccines which are being developed against SARS-CoV-2 virus are mention below in **Table 1**.

3. Conclusion

Covid-19 is a devastating situation to the whole world and this infection is the reason for the morbidity and mortality of millions of people around the globe. It has shown impact on the health, economy and social aspect of the general population. Various therapeutic agents like ACE-2, TMPRSS2, JAK–STAT, cathepsin L, furin inhibitors, antiviral drugs, corticosteroids and plasma therapy have been tried for the treatment of covid-19 infected patients; however, conflicting results are obtained during the various clinical trials in the use of some therapeutic agents. Further, various vaccination programmes through various vaccine candidates are under progress; nevertheless, it will take time to complete dosing the millions of people. Therefore, various therapeutic agents are in need and require research to tackle this SARS-CoV-2 infection.

Conflict of interest

The authors declare no conflict of interest.

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References

[1] Zhu H, Wei L, Niu P. The novel coronavirus outbreak in Wuhan, China. Global health research and policy. 2020 Dec; 5(1):1-3.

[2] Mohanty SK, Satapathy A, Naidu MM, Mukhopadhyay S, Sharma S, Barton LM, Stroberg E, Duval EJ, Pradhan D, Tzankov A, Parwani AV. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and coronavirus disease 19 (COVID-19)–anatomic pathology perspective on current knowledge. Diagnostic Pathology. 2020; 15(1):1-17.

[3] World Health Organization. COVID-19 weekly epidemiological update, 22 December 2020.

[4] Pal M, Berhanu G, Desalegn C, Kandi V. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): an update. Cureus. 2020; 12(3).

[5] Gil C, Ginex T, Maestro I, Nozal V, Barrado-Gil L, Cuesta-Geijo MÁ, Urquiza J, Ramírez D, Alonso C, Campillo NE, Martinez A. COVID-19: drug targets and potential treatments. Journal of Medicinal Chemistry. 2020; 63(21):12359-86.

[6] Lu CW, Liu XF, Jia ZF. 2019-nCoV transmission through the ocular surface must not be ignored. Lancet (London, England). 2020; 395(10224):e39.

[7] Saawarn B, Hait S. Occurrence, fate and removal of SARS-CoV-2 in wastewater: Current knowledge and future perspectives. Journal of Environmental Chemical Engineering. 2020; 104870.

[8] Dhiman R, Rakheja V, Saxena R. An Ophthalmologist's Insight Into The Viral Pandemics. Journal of Optometry. 2021 Jan 6.

[9] Flores-Alanis A, Sandner-Miranda L, Delgado G, Cravioto A, Morales-Espinosa R. The receptor binding domain of SARS-CoV-2 spike protein is the result of an ancestral recombination between the bat-CoV RaTG13 and the pangolin-CoV MP789. BMC research notes. 2020; 13(1):1-6.

[10] Kumar R, Lee MH, Mickael C, Kassa B, Pasha Q, Tuder R, Graham B. Pathophysiology and potential future therapeutic targets using preclinical models of COVID-19. ERJ Open Research. 2020; 6(4).

[11] Zhao J, Cui W, Tian BP. The potential intermediate hosts for SARS-CoV-2. Frontiers in Microbiology. 2020; 11.

[12] Zhang T, Wu Q, Zhang Z. Probable pangolin origin of SARS-CoV-2 associated with the COVID-19 outbreak. Current Biology. 2020; 30(7):1346-51.

[13] Zhang J, Xie B, Hashimoto K. Current status of potential therapeutic candidates for the COVID-19 crisis. Brain, Behavior, and Immunity. 2020 Apr 22.

[14] Prasad R. COVID-19: Current status, Challenges and Future Perspectives. 2020; 1-2.

[15] Kumar BK, Sekhar KV, Kunjiappan S, Jamalis J, Balaña-Fouce R, Tekwani BL, Sankaranarayanan M. Druggable targets of SARS-CoV-2 and treatment opportunities for COVID-19. Bioorganic Chemistry. 2020 Sep 8:104269.

[16] Baig MS, Alagumuthu M, Rajpoot S, Saqib U. Identification of a potential peptide inhibitor of SARS-CoV-2 targeting its entry into the host cells. Drugs in R&D. 2020; 20(3):161-9.

[17] Liu T, Luo S, Libby P, Shi GP. Cathepsin L-selective inhibitors:

A potentially promising treatment for COVID-19 patients. Pharmacology & Therapeutics. 2020 May 26:107587.

[18] Iwata-Yoshikawa N, Okamura T, Shimizu Y, Hasegawa H, Takeda M, Nagata N. TMPRSS2 contributes to virus spread and immunopathology in the airways of murine models after coronavirus infection. Journal of Virology. 2019; 93(6).

[19] Belouzard S, Millet JK, Licitra BN, Whittaker GR. Mechanisms of coronavirus cell entry mediated by the viral spike protein. Viruses. 2012; 4(6):1011-33.

[20] V'kovski P, Gerber M, Kelly J, Pfaender S, Ebert N, Lagache SB, Simillion C, Portmann J, Stalder H, Gaschen V, Bruggmann R. Determination of host proteins composing the microenvironment of coronavirus replicase complexes by proximity-labeling. Elife. 2019; 8:e42037.

[21] V'kovski P, Kratzel A, Steiner S, Stalder H, Thiel V. Coronavirus biology and replication: implications for SARS-CoV-2. Nature Reviews Microbiology. 2020;1-6.

[22] Saxena A. Drug targets for COVID-19 therapeutics: Ongoing global efforts. Journal of Biosciences. 2020; 45(1):1-24.

[23] Davidson AM, Wysocki J, Batlle D. Interaction of SARS-CoV-2 and other Coronavirus with ACE (Angiotensin-Converting Enzyme)-2 as their main receptor: therapeutic implications. Hypertension. 2020; 76(5):1339-49.

[24] Fu J, Zhou B, Zhang L, Balaji KS, Wei C, Liu X, Chen H, Peng J, Fu J. Expressions and significances of the angiotensin-converting enzyme 2 gene, the receptor of SARS-CoV-2 for COVID-19. Molecular Biology Reports. 2020; 47:4383-92.

[25] Wu C, Zheng S, Chen Y, Zheng M. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCoV, in the nasal tissue. MedRxiv. 2020 Jan 1.

[26] Tikellis C, Thomas MC. Angiotensin-converting enzyme 2 (ACE2) is a key modulator of the renin angiotensin system in health and disease. International journal of peptides. 2012.

[27] Gómez J, Albaiceta GM, García-Clemente M, López-Larrea C, Amado-Rodríguez L, Lopez-Alonso I, Hermida T, Enriquez AI, Herrero P, Melón S, Alvarez-Argüelles ME. Angiotensin-converting enzymes (ACE, ACE2) gene variants and COVID-19 outcome. Gene. 2020; 762:145102.

[28] Sriram K, Insel PA. A hypothesis for pathobiology and treatment of COVID-19: The centrality of ACE1/ACE2 imbalance. British Journal of Pharmacology. 2020; 177(21):4825-44.

[29] Rothlin RP, Vetulli HM, Duarte M, Pelorosso FG. Telmisartan as tentative angiotensin receptor blocker therapeutic for COVID-19. Drug Development Research. 2020; 81(7): 768-770.

[30] Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. Nature Medicine. 2005; 11(8):875-9.

[31] Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Medicine. 2020; 46(4):586-90.

[32] Mukhopadhyay D, Mussa BM. Identification of novel hypothalamic microRNAs as promising therapeutics

for SARS-CoV-2 by regulating ACE2 and TMPRSS2 expression: an in silico analysis. Brain Sciences. 2020; 10(10):666.

[33] Kawase M, Shirato K, van der Hoek L, Taguchi F, Matsuyama S. Simultaneous treatment of human bronchial epithelial cells with serine and cysteine protease inhibitors prevents severe acute respiratory syndrome coronavirus entry. Journal of Virology. 2012; 86(12):6537-45.

[34] Matsuyama S, Nagata N, Shirato K, Kawase M, Takeda M, Taguchi F. Efficient activation of the severe acute respiratory syndrome coronavirus spike protein by the transmembrane protease TMPRSS2. Journal of Virology. 2010; 84(24):12658-64.

[35] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020; 181(2):271-80.

[36] Shen LW, Mao HJ, Wu YL, Tanaka Y, Zhang W. TMPRSS2: A potential target for treatment of influenza virus and coronavirus infections. Biochimie. 2017;142:1-10.

[37] Maggio R, Corsini GU. Repurposing the mucolytic cough suppressant and TMPRSS2 protease inhibitor bromhexine for the prevention and management of SARS-CoV-2 infection. Pharmacological Research. 2020; 157:104837.

[38] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020; 395(10223):497-506.

[39] Seif F, Aazami H, Khoshmirsafa M, Kamali M, Mohsenzadegan M, Pornour M, Mansouri D. JAK inhibition as a new treatment strategy for patients with COVID-19. International Archives of Allergy and Immunology. 2020; 181(6):467-75.

[40] Júnior ML, de Souza LM, Dutra RE, de Melo Valente RG, Melo TS. Review on therapeutic targets for COVID-19: insights from cytokine storm. Postgraduate Medical Journal. 2020.

[41] Liu CL, Guo J, Zhang X, Sukhova GK, Libby P, Shi GP. Cysteine protease cathepsins in cardiovascular disease: from basic research to clinical trials. Nature Reviews Cardiology. 2018; 15(6):351-70.

[42] Meyer D, Sielaff F, Hammami M, Böttcher-Friebertshäuser E, Garten W, Steinmetzer T. Identification of the first synthetic inhibitors of the type II transmembrane serine protease TMPRSS2 suitable for inhibition of influenza virus activation. Biochemical Journal. 2013; 452(2):331-43.

[43] Ou X, Liu Y, Lei X, Li P, Mi D, Ren L, Guo L, Guo R, Chen T, Hu J, Xiang Z. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nature Communications. 2020 Mar 27; 11(1):1-12.

[44] Hoffmann M, Schroeder S, Kleine-Weber H, Müller MA, Drosten C, Pöhlmann S. Nafamostat mesylate blocks activation of SARS-CoV-2: new treatment option for COVID-19. Antimicrobial Agents and Chemotherapy. 2020.

[45] Belen-Apak FB, Sarialioglu F. The old but new: Can unfractioned heparin and low molecular weight heparins inhibit proteolytic activation and cellular internalization of SARS-CoV2 by inhibition of host cell proteases. Medical Hypotheses. 2020; 142:109743.

[46] Wu C, Zheng M, Yang Y, Gu X, Yang K, Li M, Liu Y, Zhang Q, Zhang P, Wang Y, Wang Q. Furin: A Potential Therapeutic Target for COVID-19. Iscience. 2020; 23(10):101642.

[47] Fitzgerald K. Furin Protease: From SARS CoV-2 to Anthrax, Diabetes, and Hypertension. The Permanente Journal. 2020; 24.

[48] Uludağ H, Parent K, Aliabadi HM, Haddadi A. Prospects for RNAi therapy of COVID-19. Frontiers in Bioengineering and Biotechnology. 2020; 8:916.

[49] Ghosh S, Firdous SM, Nath A. siRNA could be a potential therapy for COVID-19. EXCLI Journal. 2020; 19:528.

[50] Huang Y, Yang C, Xu XF, Xu W, Liu SW. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacologica Sinica. 2020; 41(9):1141-9.

[51] Xia S, Liu M, Wang C, Xu W, Lan Q, Feng S, Qi F, Bao L, Du L, Liu S, Qin C. Inhibition of SARS-CoV-2 (previously 2019-nCoV) infection by a highly potent pan-coronavirus fusion inhibitor targeting its spike protein that harbors a high capacity to mediate membrane fusion. Cell Research. 2020; 30(4):343-55.

[52] Jin Z, Du X, Xu Y, Deng Y, Liu M, Zhao Y, Zhang B, Li X, Zhang L, Peng C, Duan Y. Structure of M pro from SARS-CoV-2 and discovery of its inhibitors. Nature. 2020; 582(7811):289-93.

[53] Macchiagodena M, Pagliai M, Procacci P. Identification of potential binders of the main protease 3CLpro of the COVID-19 via structure-based ligand design and molecular modeling. Chemical Physics Letters. 2020; 750:137489.

[54] Bhatnagar T, Murhekar MV, Soneja M, Gupta N, Giri S, Wig N, Gangakhedkar R. Lopinavir/ritonavir combination therapy amongst symptomatic coronavirus disease 2019 patients in India: Protocol for restricted public health emergency use. Indian Journal of Medical Research. 2020; 151(2):184.

[55] Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, Wang Q, Xu Y, Li M, Li X, Zheng M. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharmaceutica Sinica B. 2020; 10(5):766-88.

[56] Malin JJ, Suárez I, Priesner V, Fätkenheuer G, Rybniker J. Remdesivir against COVID-19 and other viral diseases. Clinical microbiology reviews. 2020; 34(1).

[57] Monteleone G, Sarzi-Puttini PC, Ardizzone S. Preventing COVID-19-induced pneumonia with anticytokine therapy. The Lancet Rheumatology. 2020; 2(5):e255-6.

[58] Rahmati M, Moosavi MA. Cytokine-targeted therapy in severely ill COVID-19 patients: options and cautions. Mortality. 2020; 105954.

[59] Chi Zhang MD, Zhao Wu PD, Jia-Wen Li MD. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor antagonist Tocilizumab may be the key to reduce mortality. International Journal of Antimicrobial Agents. 2020; 105954(10.1016).

[60] Duret PM, Sebbag E, Mallick A, Gravier S, Spielmann L, Messer L. Recovery from COVID-19 in a patient with spondyloarthritis treated with TNF-alpha inhibitor etanercept. Annals of the Rheumatic Diseases. 2020; 79(9):1251-2.

[61] Calabrese LH, Calabrese C. Cytokine release syndrome and

the prospects for immunotherapy with COVID-19. Part 2: The role of interleukin 1. Cleveland Clinic Journal of Medicine. 2020 Jul 9. DOI: https://doi.org/10.3949/ccjm.87a.ccc044.

[62] Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, Oltolini C, Castiglioni B, Din CT, Boffini N, Tomelleri A. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. The Lancet Rheumatology. 2020; 2(6):e325-31.

[63] Nile SH, Nile A, Qiu J, Li L, Jia X, Kai G. COVID-19: Pathogenesis, cytokine storm and therapeutic potential of interferons. Cytokine & Growth Factor Reviews. 2020; 53:66-70.

[64] Eastman RT, Roth JS, Brimacombe KR, Simeonov A, Shen M, Patnaik S, Hall MD. Remdesivir: a review of its discovery and development leading to emergency use authorization for treatment of COVID-19. ACS Central Science. 2020; 6(5):672-83.

[65] McKee DL, Sternberg A, Stange U, Laufer S, Naujokat C. Candidate drugs against SARS-CoV-2 and COVID-19. Pharmacological research. 2020 Apr 29:104859.

[66] Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, Feldt T, Green G, Green ML, Lescure FX, Nicastri E. Compassionate use of remdesivir for patients with severe Covid-19. New England Journal of Medicine. 2020 ;382(24):2327-36.

[67] Hung IF, Lung KC, Tso EY, Liu R, Chung TW, Chu MY, Ng YY, Lo J, Chan J, Tam AR, Shum HP. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. The Lancet. 2020; 395(10238):1695-704.

[68] Delang L, Abdelnabi R, Neyts J. Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. Antiviral research. 2018; 153:85-94.

[69] Belete TM. An Up-to-Date Overview of Therapeutic Agents for the Treatment of COVID-19 Disease. Clinical pharmacology: advances and applications. 2020; 12:203.

[70] Zha L, Li S, Pan L, Tefsen B, Li Y, French N, Chen L, Yang G, Villanueva EV. Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19). Medical Journal of Australia. 2020; 212(9):416-20.

[71] van Paassen J, Vos JS, Hoekstra EM, Neumann KM, Boot PC, Arbous SM. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. Critical Care. 2020; 24(1):1-22.

[72] Wu C, Chen X, Cai Y, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Internal Medicine. 2020; 180(7):934-43.

[73] Mishra GP, Mulani J. Corticosteroids for COVID-19: the search for an optimum duration of therapy. The Lancet. Respiratory Medicine. 2021; 9(1):e8.

[74] Wang X, Guo X, Xin Q, Pan Y, Hu Y, Li J, Chu Y, Feng Y, Wang Q. Neutralizing antibodies responses to SARS-CoV-2 in COVID-19 inpatients and convalescent patients. Clinical Infectious Diseases. 2020.

[75] Bloch EM, Shoham S, Casadevall A, Sachais BS, Shaz B, Winters JL, Van Buskirk C, Grossman BJ, Joyner M, Henderson JP, Pekosz A. Deployment of convalescent plasma for the prevention and treatment of COVID-19.

The Journal of clinical investigation. 2020; 130(6):2757-65.

[76] Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, Zhou M, Chen L, Meng S, Hu Y, Peng C. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proceedings of the National Academy of Sciences. 2020;117(17):9490-6.

[77] Salazar E, Perez KK, Ashraf M, Chen J, Castillo B, Christensen PA, Eubank T, Bernard DW, Eagar TN, Long SW, Subedi S. Treatment of coronavirus disease 2019 (COVID-19) patients with convalescent plasma. The American Journal of Pathology. 2020; 190(8):1680-90.

[78] Trivedi N, Verma A, Kumar D. Possible treatment and strategies for COVID-19: review and assessment. European Review for Medical and Pharmacological Sciences. 2020; 24(23):12593-608.

[79] Padhy BM, Mohanty RR, Das S, Meher BR. Therapeutic potential of ivermectin as add on treatment in COVID 19: A systematic review and meta-analysis: Ivermectin in COVID-19: A meta-analysis. Journal of Pharmacy & Pharmaceutical Sciences. 2020; 23:462-9.

[80] Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Research. 2020; 178:104787.

[81] Choudhary R, Sharma AK. Potential use of hydroxychloroquine, ivermectin and azithromycin drugs in fighting COVID-19: trends, scope and relevance. New Microbes and New Infections. 2020:100684.

[82] dos Reis Neto ET, Kakehasi AM, de Medeiros Pinheiro M, Ferreira GA, Marques CD, da Mota LM, dos Santos Paiva E, Pileggi GC, Sato EI, Reis AP, Xavier RM. Revisiting hydroxychloroquine and chloroquine for patients with chronic immunity-mediated inflammatory rheumatic diseases. Advances in Rheumatology. 2020; 60(1):1-1.

[83] Jorge A. Hydroxychloroquine in the prevention of COVID-19 mortality. The Lancet Rheumatology. 2021; 3(1):e2-3.

[84] Juurlink DN. Safety considerations with chloroquine, hydroxychloroquine and azithromycin in the management of SARS-CoV-2 infection. Canadian Medical Association Journal. 2020; 192(17):E450-3.

[85] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Research. 2020; 30(3):269-71.

[86] Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clinical Infectious Diseases. 2020; 71(15):732-9.

[87] Rentsch CT, DeVito NJ, MacKenna B, Morton CE, Bhaskaran K, Brown JP, Goldacre B. Effect of pre-exposure use of hydroxychloroquine on COVID-19 mortality: a population-based cohort study in patients with rheumatoid arthritis or systemic lupus erythematosus using the Open SAFELY platform. The Lancet Rheumatology, 2021; 3(1): e19-e27.

[88] Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, Labella A, Manson DK, Kubin C, Barr RG, Sobieszczyk ME. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. New England Journal of Medicine. 2020; 382(25):2411-8.

[89] Yadav T, Srivastava N, Mishra G, Dhama K, Kumar S, Puri B, Saxena SK. Recombinant vaccines for COVID-19. Human Vaccines & Immunotherapeutics. 2020; 16(12):2905-12.

[90] Krammer F. SARS-CoV-2 vaccines in development. Nature. 2020; 586(7830):516-27.

[91] Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, Li Y, Zhu L, Wang N, Lv Z, Gao H. Development of an inactivated vaccine candidate for SARS-CoV-2. Science. 2020; 369(6499):77-81.

[92] Tumban E. Lead SARS-CoV-2 Candidate Vaccines: Expectations from Phase III Trials and Recommendations Post-Vaccine Approval. Viruses. 2021;13(1):54

[93] Tregoning JS, Brown ES, Cheeseman HM, Flight KE, Higham SL, Lemm NM, Pierce BF, Stirling DC, Wang Z, Pollock KM. Vaccines for COVID-19. Clinical & Experimental Immunology. 2020; 202(2):162-92.

[94] COVAXIN® -India's first indigenous COVID-19 vaccine. Bharat Biotech. (http://www.bharatbiotech.com).

[95] Batty CJ, Heise MT, Bachelder EM, Ainslie KM. Vaccine formulations in clinical development for the prevention of severe acute respiratory syndrome coronavirus 2 infection. Advanced Drug Delivery Reviews. 2020 Dec 13.

[96] Inovio expects to begin late-stage COVID-19 vaccine study in second quarter. Thomson Reuters Foundation news, 10 Feb, 2021.

[97] Buschmann MD, Carrasco MJ, Alishetty S, Paige M, Alameh MG, Weissman D. Nanomaterial Delivery Systems for mRNA Vaccines. Vaccines. 2021; 9(1):65.

[98] Moderna announces primary efficacy analysis in phase 3 COVE study for its COVID-19 vaccine candidate and filing today with U.S. FDA for emergency use authorization. Moderna Press Release. November 30, 2020.

[99] Oliver SE, Gargano JW, Marin M, Wallace M, Curran KG, Chamberland M, McClung N, Campos-Outcalt D, Morgan RL, Mbaeyi S, Romero JR. The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine—United States, December 2020. Morbidity and Mortality Weekly Report. 2020 ; 69(50):1922.

[100] Dai L, Gao GF. Viral targets for vaccines against COVID-19. Nature Reviews Immunology. 2020;1-10.

[101] Novavax to seek EUA for covid-19 vaccine as early as april. Medscape Medical News, 26 Feb, 2021. (https://www.medscape.com/viewarticle/946422).

[102] Ng WH, Liu X, Mahalingam S. Development of vaccines for SARS-CoV-2. F1000Research. 2020; 9.

[103] WHO gives emergency use approval to AstraZeneca-Oxford's COVID-19 vaccine. Business Today. 15 Feb, 2021. (https://www.businesstoday.in/current/economy-politics/who-gives-emergency-use-approval-to-astrazeneca-oxford-covid-19-vaccines/story/431366.html)

[104] Nikhra V. Stages in COVID-19 Vaccine Development: The Nemesis, the Hubris, and the Elpis. International Journal Clinical Virology. 2020; 4:126-35.