Pathogenesis, Diagnosis and Possible Therapeutic Options for COVID-19

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Abstract

The recent pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread so rapidly and severely affected the people of almost every country in the world. The highly contagious nature of this virus makes it difficult to take control of the present pandemic situation. With no specific treatment available, the coronavirus disease 2019 (COVID-19) presents a threat to people of all ages including the elderly people and people with other medical complications as a vulnerable group to this disease. Better understanding of viral pathogenesis, appropriate preventive measures, early diagnosis and supportive treatments of the infected patients are now the general solutions to fight against this viral transmission. But, as an emerging disease, most about it remains still poorly understood. This article holds an overview on the origin and structure, pathogenesis, diagnosis and possible therapeutic options for the causative agent, SARS-CoV-2 and disease, COVID-19. However, few therapeutic options, laboratory experiments and other strategies proposed here need to be further clinically tested.

Keywords: COVID-19; Diagnosis; Pathogenesis; Treatment; SARS-CoV-2

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1. Introduction

The severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) known to cause coronavirus disease 2019 (COVID-19), is rapidly spreading from its origin in Wuhan City of Hubei Province of China to the rest of the world [1]. Over the past few decades, a large number of people have been affected with the 3 epidemics caused by coronavirus family in the world. In the previous epidemics, initial hotspots of diseases were Middle East, Saudi Arabia (Middle East Respiratory Syndrome coronavirus (MERS-CoV) and China (SARS-CoV) where animal to human, and then human to human transmissions of pathogens were reported in other countries [2][3]. For COVID-19, as suggested by epidemiological evidence in China, this outbreak began from a seafood and live animal shopping center in Wuhan, Hubei Province on December 12, 2019 [4]. Number of COVID-19 cases has risen substantially in the world compared to SARS and MERS, and it would probably take longer to halve the disease cases; meaning that control measures would have to be in place for a longer period of time [5]. On 12 March, 2020, WHO declared COVID-19 as pandemic pointing the spread of the virus in more than hundred countries [6]. Coronaviruses are a group of highly diverse, enveloped, positive-sense, single-stranded RNA viruses. They cause several diseases of respiratory, enteric, hepatic and neurological systems with varying severity among humans and animals [7][8]. Human coronavirus (CoV) infections have traditionally caused a low percentage of annual respiratory infections. According to serology and genome phylogeny, coronaviruses are classified into four genera termed Alpha, Beta, Gamma and Delta coronavirus. So far, seven human coronaviruses have been determined, containing two alpha CoVs (HCoV-229E and HCoV-NL63) and five beta CoVs (HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV and SARS-CoV [9]. Over the past two decades, three coronaviruses, SARS-CoV,MERS-CoVand SARS-CoV-2 have emerged and caused severe human diseases [10][11].There are some overlapping and discrete aspects of the pathology and

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pathogenesis of these coronaviruses which cause severe lung diseases in humans owing to death in critical case [12]. As of April 13, 2020, SARS-CoV-2 has spread in 210 countries and territories around the world and 2 international conveyances and taken more than one hundred thousand lives with almost 1.8 million more infected cases [13]. Understanding the pathogenesis of SARS-CoV-2 infection, early diagnosis and supportive treatments are crucial to combat the outbreak of this highly contagious virus. This article includes an overview on molecular pathogenesis, diagnosis and possible therapeutic options for COVID-19 which should hold a scientific understanding necessary to prevent the viral transmission.

2. Origin and Characteristics of SARS-CoV-2

The novel coronavirus, commonly known to cause COVID-19, is delineated as novel pneumonia that occurs due to infection by a strain that was initially detected in Wuhan, Hubei province, China [14]. Name of the strain and disease was first introduced by The International Committee on Taxonomy of Viruses (ICTV). That particular strain was called SARS-CoV-2 and the disease was designated as COVID-19 [15]-[19]. This novel virus is one type of β-coronavirus that is enveloped, non-segmented and positive-sense RNA virus (subgenus *sarbecovirus*, *Orthocoronavirinae* subfamily) [20].

According to the current researches, the first case of corona virus infection in human was discovered in 17 November, 2019 [21]. The authentic source of this patgogen's transmission to humans still seems obscure [22]-[24]. It has been suggested that, the strain might have been originated from the Huanan Seafood Market where bats, snakes, raccoon dogs, palm civets, and other animals are sold. From the wet market it rapidly spread up to 210 countries and territories around the world by April 12, 2020 [25]. The workers at the market were the first to be detcted with this disease [26][27]. There was also a prediction which claims that the visitors, not the

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workers, were the ones who introduced the disease to the market. Later, the disease was transmitted over the mass population [22][28]. Notwithstanding, there is no confirmed information which manifests that SARS-CoV-2 was originated from that wet market.

Certainly, bats are considered as the natural reservoir of broad and diversified range of CoVs. However, to find out the origin of SARS-CoV-2 the natural reservoir of SARS-CoV, which caused the previous 2002-2004 SARS outbreak, was analyzed. The analysis resulted in the discovery of many SARS-like bat coronaviruses which were predominantly originated in the *Rhinolophus* genus of horseshoe bats. SARS-CoV-2 and two viral RNA sequences found in samples taken from *Rhinolophus sinicus*demonstrated approximately 80% similarity to SARS-CoV-2 [29]-[31]. Moreover, another RNA sequence of *Rhinolophus affinis*(RaTG13), found in Yunnan province, has a 96.2% analogy with SARS-CoV-2 [32][33].Consequently, bats are contemplated as the most probable natural reservoir of SARS-CoV-2 [34][35]. Inspite of all these significant difference lies between the bat coronavirus and SARS-CoV-2. Similarly contrasting features between SARS-CoV and SARS-CoV-2 have also been noticed according to genomic analysis. Though SARS-CoV-2 shares 79.5% genomic identity to SARS-CoV, five of the total six amino acids of receptor-binding domain(RBD) of S protein that are crucial for binding to human receptor - ACE2 were found to differ between them. But still according to the structural studiesand biochemical experiments, RBD of SARS-Cov-2 appears to have high affinity to bind with human ACE2. However, it has now been clarified that, this virus has not been originated by any purposeful laboratory manipulation [15]-[20][36][37].Also, there exists an unrecognized intermediate host by which viral transmission took place from bat to human via recombination [38].

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Some primary reports state that two species of snakes also could be probable reservoir of disease COVID-19. However, there exists no strong evidence of coronavirus reservoirs other than mammals and birds. Again, genomic analysis predicts that there is another source which is significantly identical with the viral RNA sequence. Pangolin-CoV and SARS-CoV-2 have been proved to have 99% similarity in the receptor –binding domain of the S protein [21][24][39]. Inspite of all these, thesimilarity of *pangolin*-Cov to SARS-CoV-2 is not as much as the analogy of RaTG13 to SARS-CoV-2 [40]. That is because *pangolin*-CoV shares only 92% of their complete genomes with SARS-CoV-2. Hence, it is inadequate to prove the effectiveness of pangolin as an intermediate host. A metagenomic study of 2019 depicts that,SARS-CoV was the most widely distributed coronavirus among a sample of *Sunda pangolins*[41]. Thus, they might act as an intermediate host and went through recombination and then infected humans. According to another study, recombination in the host intermediate of novel corona virus actively facilitated the virus to attain accelerated rate of transmission compared to SARS-CoV. Moreover, analysis of homolgous recombination illustrates that receptor binding spike glycoprotein of novel coronavirus evolved from a SARS-CoV (CoVZXC21 or CoVZC45) and an unidentified Beta-CoV. Therefore, we are anticipating to detect the authentic intermediate host via which the virus was directly transmitted to humans.

SARS CoV-2 genome was elucidated to contain 14 open reading frames (ORFs) encoding 27 proteins. At the 5′-terminus of the genome, two genes are located namely: orf1ab (encodes pp1ab protein) and orf1a (encodes for pp1a protein). Altogether, they constitute 16 non-structural proteins (nsps) (nsp1-nsp10 and nsp12-nsp16) (**Figure 01**). Genes at the 3' terminus encode for structural proteins including Hemagglutinin Esterase (HE) (found in beta-CoVs), Spike (S), Small Membrane (E), Membrane (M), Nucleocapsid (N) and Internal (I) protein. Nucleocapsid

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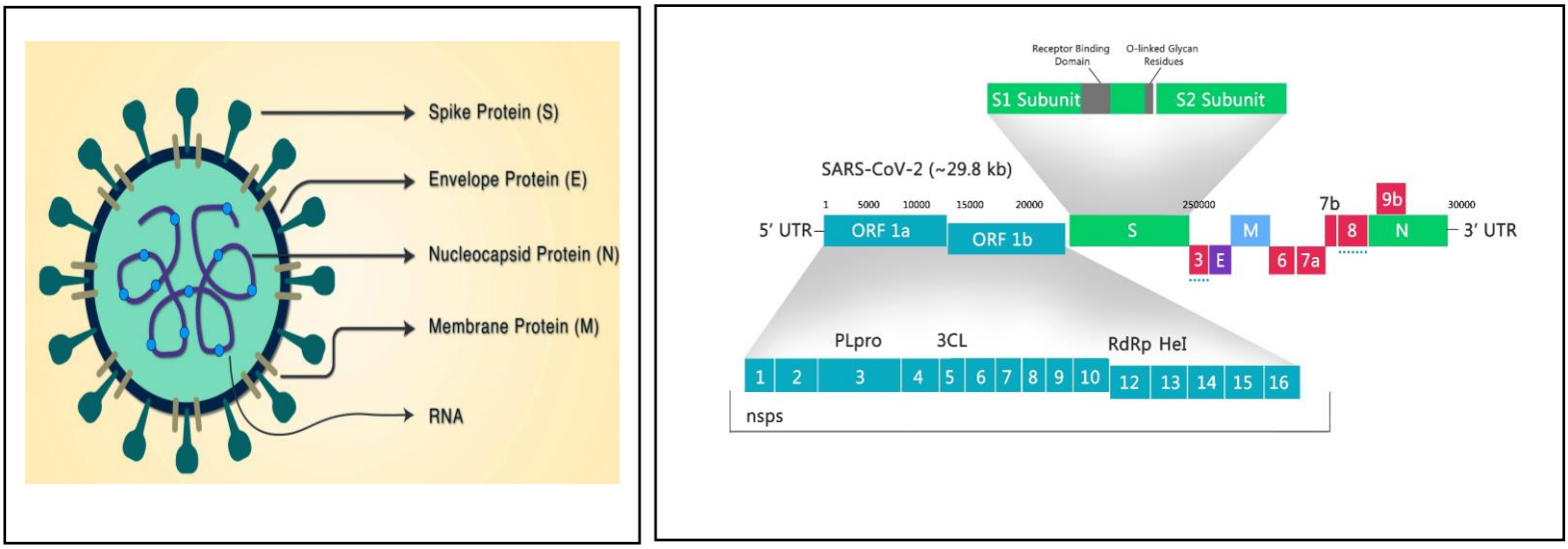
protein complexes and viral RNA and together develop a helical capsid shape. Formation of peplomers integrated in the envelope and finally giving it a corona or crown shape peplomers which is done by Spike protein trimers [38][42]. In some cases, trasmembrane protein HE forms small spikes. “M” and “E” protein work for virus assembly. Structural proteins also include eight accessory proteins: 3a, 3b, p6, 7a, 7b, 8b, 9b, and orf14. If compared at amino acid level, the sequence of SARS-CoV-2 is almost same as that of SARS-CoV. Still, some significant dissimilarities between them were found. For instance: The 8a protein is common for SARS-CoV, but in 2019-nCoV, it is absent. The 8b protein of SARS-CoV has 84 amino acids, whereas, that of SARS-CoV-2 is much longer(121 amino acids). The 3b protein of SARS-CoV comprises of 154 amino acid, but in case of 2019-nCoV, it is very much shorter(only 22 amino acids). Through further studies, it is possible to determine how the differences influence the activity and degree of pathogenicity of SARS-CoV-2 [42][43].



(A) (B)

Figure 01: (A) Typical structure of SARS-CoV-2; (B) organization of SARS-CoV-2 viral genome. 3CL: 3-chymotripsin-like protease; PLpro: Papain-like protease; RdRp: RNA-dependent RNA polymerase. HeI: Helicase.

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3. Pathogenesis of SARS-CoV-2 Infection

3.1. Mode of SARS-CoV-2 Transmission and Viral Entry Inside the Cell

Wild animals including bats are the possible hosts and reservoirs of the SARS-CoV-2. The human-to-human transmission of SARS-CoV-2 is achieved mainly via respiratory droplets of an infected individual. However, the virus can also be transmitted through the aerial droplets and contact even with an asymptomatic COVID-19 patient [44]-[46]. The presence of this virus has also been reported in the feces of the COVID-19 patient but whether the virus from feces can cause the disease or not is still poorly understood [47].

After entering the human body, SARS-CoV-2 first enters the cells of the host before replication. The first step in viral entry to human cell is the binding of a viral trimeric protein called spike protein with the human receptor angiotensin converting enzyme 2 (ACE2) (**Figure 02**). These spike proteins protruding from the membrane of the virus are responsible for the characteristic shape of the virus. TheACE2 receptor is responsible for the entry of both SARS-CoV-2 and SARS-CoV inside the cells of human body [48]. The viral spike proteins mediate the van der Waals interaction with ACE2 receptors during the viral entry which is a critical step in the manifestation of viral infection. Another type of proteins called transmembrane protease serine 2 (TMPRSS2) is required for initial priming of the spike protein with the ACE2 receptor [49]. After the receptor binding and processing by TMPRSS2 the virus enters the host cell via endocytosis.The SARS-CoV-2 and SARS-CoV spike proteins have almost 77% sequence identity and importantly a high degree of homology [50]. Recent study suggests that, the SARS-CoV-2 spike protein can bind with ACE2 receptors more effectively than that of SARS-CoV and hence the SARS-CoV-2 might be more effective in invading the human cells than SARS-CoV [51]. After entering the cell, the virus triggers replication to produce multiple copies of viral

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materials and after assembly it lyses the infected cells to get out in multiple copies and continue the infection of more healthy cells.

3.2. Replication of Coronavirus inside Human Body

The genome of coronavirus is a single-stranded positive sense RNA of approximately 30 kilobase size with typical 5′-cap and 3′-poly A tail structures. The whole genomic RNA serves as a template for the translation of replicase-transcriptase protein encoded in two open reading frames (ORFs) i.e., ORF1a and ORF1b. The replicase-transcriptase proteins are initially encoded as two large polyproteins i.e., pp1a and pp1b (**Figure 01**) [52]. These polyproteins are cleaved during or after the synthesis by virus-encoded proteinases i.e., papain like and chymotrypsin like proteases into 15 nonstructural viral proteins i.e., nsp1 to nsp10 encoded in ORF1a and nsp12 to nsp16 encoded in ORF1ab. These non-structural proteins together with other viral proteins and possibly with cellular proteins aggregate with membrane-bound replication-transcription complex (RTC) [42][53]. The RTC binds to the regulatory sequences that reside inside the coronavirus genome and may continuously copy the whole genome into a genome-length template or discontinuously into several subgenome length RNA template. These various length subgenomic RNAs then serve as the template for the production of subgenomic mRNAs [54]. The termination of transcription of subgenome mRNAsand the further acquisition of a leader RNA occurs at the transcription regulatory sequences present in the ORFs [55]. These mRNAs are then translated into different proteins required for virus assembly i.e., spike proteins, membrane glycoproteins, nucleocapsid proteins. After assembly of new viruses in multiple copies, they lyse the infected cells and get outside and continue to infect new healthy cells. So overall, the coronavirus mediates its infection in few typical steps: (i) Transmission inside human body and binding of virus spike protein with ACE2 receptors of cell membrane, (ii) Membrane

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fusion of the virus through endocytosis and release of the viral genome inside cell, (iii) Synthesis of RTC and replication of viral RNA, (iv) Transcription of subgenomic mRNAs, (v) Translation of the viral proteins, (vi) Assembly of new virions, (vii) Release of virion from infected cells via exocytosis and infect new healthy cells(**Figure 02**)[56]. Thus, the virus continues to infect new healthy cells continually which leads to progressive lung damage that characterizes the pneumonia owing to multiple organ failure and death in very critical cases. Release of virus outside of the cells in the lungs result in the aggregation of immune cells which produce abundant immune mediators and lead to acute inflammation.

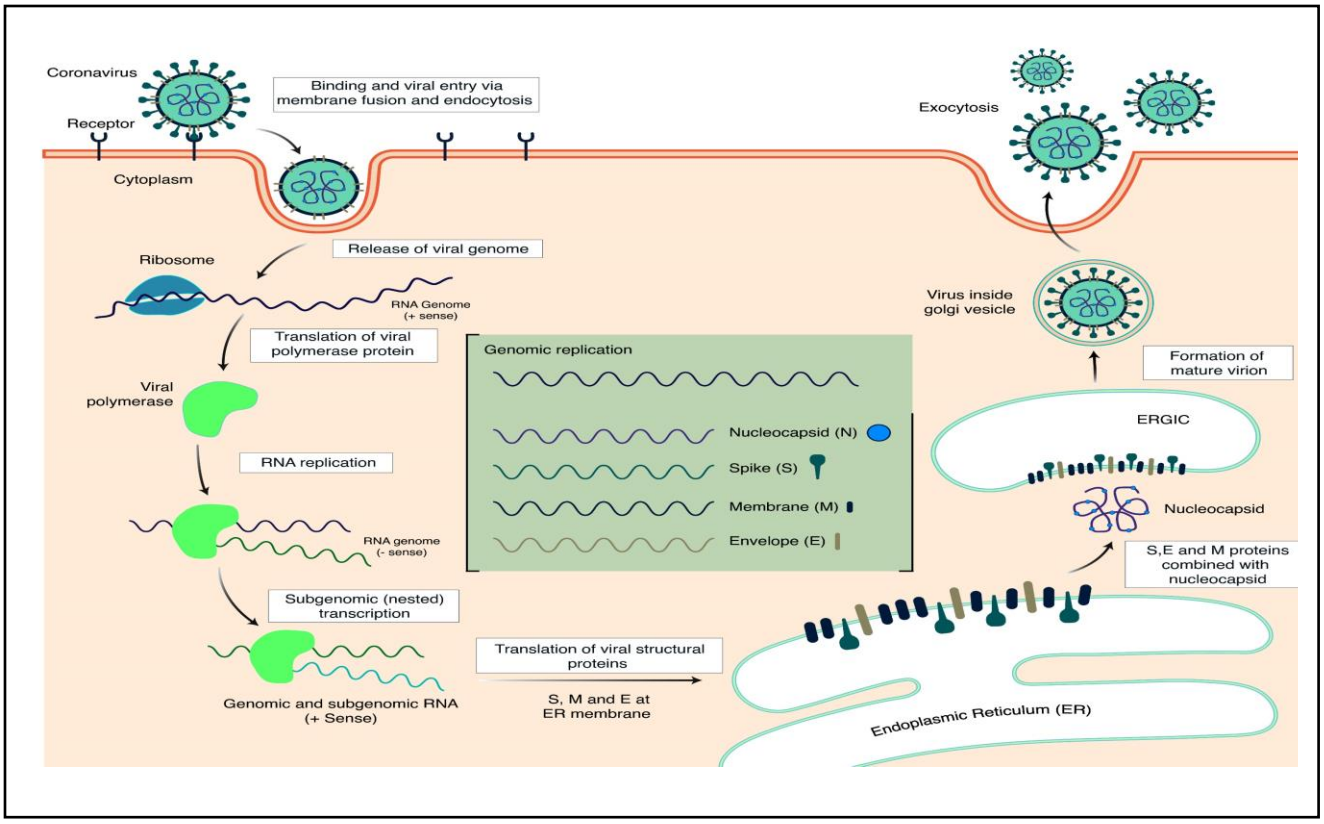

Figure 02: Reproductive cycle of SARS-CoV-2 in mediating the viral pathogenesis. Virus enters the cells via exocytosis after binding to ACE2 receptor and then replicate their genome in multiple copies and transcribe viral proteins. After assembly of virions, they lyse the host cells and get outside of the infected cells via endocytosis and the newly formed viruses infect more healthy cells. ER: Endoplasmic reticulum; ERGIC: Endoplasmic reticulum-Golgi intermediate complex.

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3.3. Human Immune Responses Against the SARS-CoV-2 and Other SARS-related Viral Infection

As an emerging disease, most about the immune response of COVID-19 inside human body remains poorly understood. Viral RNAs are recognized by the components of innate immune systems that include three major classes of cell surface receptors i.e., Toll-like receptors (TLRs), RIG-I-like receptors (RLRs) and NOD-like receptors (NLRs), which initiate the expression of interferon (IFN) and activation of anti-viral effectors of both innate and adaptive immunity i.e., Natural Killer cells, T CD8+ cells and macrophages [57]-[60].

Elevated amounts of cytokines (cytokine storm) was observed in SARS patients. SARS-CoV infection of dendritic cells (DCs) induces low-level expression of antiviral cytokines Interferon-α and β (IFN-αβ), moderate up-regulation of pro-inflammatory cytokines i.e., tumor necrosis factor (TNF) and interleukin-6 (IL-6), and a significant up-regulation of inflammatory chemokines C-C Motif Chemokine Ligand 3 (CCL3), CCL5, CCL2, and C-X-C motif chemokine 10(CXCL10) [61][62]. Moreover, Pro-inflammatory cytokines Interferon- γ (IFN-γ), IL-1, IL-6, IL-12, and Transforming growth factor β (TGFβ) and chemokines i.e., CCL2, CXCL10, CXCL9, and IL-8 were also found in elevated amounts in severe SARS disease patient compared to mild patient. Conversely, SARS patients with severe disease were reported to have very low levels of the anti-inflammatory cytokine, IL-10(**Table 01**) [63]-[66].

In vitro and *in vivo* experiments on MERS infection suggests the release of increased amount cytokines and chemokines i.e., CCL-2, CCL-3, CCL-5, IL-2, and IL-8 by different immune cells [67][68]. Elevated levels of serum pro-inflammatory cytokines i.e., IL-6 and IFN-α and

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chemokines i.e., IL-8, CXCL-10, and CCL5 were also observed in individuals with severe MERS compared to patients with mild disease [69][70].

A recent study has found increased expressions of cytokines i.e., IL-6, IL-10, and TNFα, lymphopenia in both types of T cellsbutdecreased expression of IFN-γ in patients with severe COVID-19 [71]. Another study has found significantcorrelation between elevated level of CXCL10, monocyte chemotactic protein-3 (MCP-3), IL-1ra and severity and progression of COVID-19 [72]. Increased plasma levels of IL-2, IL-7, Granulocyte-colony stimulating factor (GCSF), MCP-1 and Macrophage Inflammatory Protein-1a (MIP-1a) has also been found in severe cases of COVID-19 [73][74].

Disease	Cytokines and Chemokines		References
	Elevated	Decreased	
SARS	TNF, IL-6, CCL3, CCL5, CCL2, CXCL10, IFN-γ, IL-1, IL-6, IL-12, TGFβ, CCL2, CXCL10, CXCL9 and IL-8	IL-10, IFN-α, IFN-β	[61]-[66]
MERS	CCL-2, CCL-3, CCL-5, IL-2, IL-8, CXCL-10, IL-6	-	[67]-[70]
COVID-19	IL-6, IL-10, TNFα, CXCL10 IL-2, Il-7, GSCF, MCP-1 and MIP-1a	IFN-γ	[71]-[74]

Table 01: Elevated and decreased cytokines and chemokines in different disease caused by SARS-related coronaviruses.

4. Diagnosis of COVID-19 Patient

Initially the COVID-19 patients are identified on the basis of presence of clinical symptoms associated with primary stage of disease progression. But confirmatory test of the COVID-19 patient can be achieved by variety of methods i.e., nucleic acid-based identification, computed tomography scan (CT scan), immune-reaction based techniques in the laboratory (**Table 02**).

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4.1. Real-time Quantitative Polymerase Chain Reaction (RT-qPCR)

RT-qPCR provides an efficient method for the detection of the presence of the virus in COVID-19 patients. The technique involves the viral RNA extraction from the respiratory samples, oropharyngeal swab, salivaof the COVID-19 patients. Then the specific sequence in viral genome is amplified in multiple copiesin conventional manner in the presence of reaction buffer, Taq polymerase, master mix in a thermal cycler under appropriate conditions [75]. Different gene sequences can be targeted as the intended amplicons i.e., RdRp gene: RNA-dependent RNA polymerase gene, E gene: envelope protein gene, M gene: membrane protein gene, N gene: nucleocapsid protein gene, S gene: spike protein gene or other open reading frame (ORF) gene. The amplification of any of these gene can be achieved by providing appropriate forward and reverse primers. A recent study has found 95% sensitivity of the PCR amplification of E and RdRp gene rom SARS coronavirus [76]. Another study suggested that, the presence of SARS-CoV-2 virus can be detected from the stool of the infected patient using the nucleic-acid based detection techniques. Again, the same study found negative results with both nucleic acid-based tests and test kits from the urine and blood sample of the patient. This is might be due to the low concentration of the virus in those samples [77]. Another study found 91.7% positive rates (11/12 patients) in RT-qPCR test using saliva sample from COVID-19 patients, suggesting that saliva could be a non-invasive sample from the infected patient [78]. However, although the RT-qPCR is an effective technique for the identification of SARS-CoV-2 virus from COVID-19 patients but it may come out with false positive results sometime and the technique itself is highly laborious and involves the management of biohazards.

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4.2. CT Scan Imaging

Although the RT-qPCR is a specificSARS-CoV-2 detection technique but the chance of false positive results can not be ignored. Therefore, many clinicians offer the use of CT scan but use of the combination of both techniques is more helpful and thus CT scan can assist the mass identification in a heavilyinfected area. A recent study suggested that, CT scan is more sensitive in the detection of SARS-CoV-2 virus from COVID-19 patient than the PCR-based method [79]. Moreover, high resolution CT (HRCT) can be used effectively for the initial identification of the COVID-19 patient [80]. The technique utilizes narrow X-ray beam that circles around the body parts of the patient and provides a series of picture form different angles. A computer program then combines the multiple captures to provide a cross-sectional image. CT scan of COVID-19 patient showed abnormal image with the sign of bilateral multiple ground-glass opacities or consolidation in recent studies [81][82]. Other findings also suggested the involvement of ground-glass opacities is a common phenomenon in COVID-19 patient and the involvement of multilobes in the chest of CT image of COVID-19 patient was also observed in the same study. But other lung abnormalities i.e., lung cavitation, discrete pulmonary nodules, pleural effusions, and lymphadenopathy were absent [83][84]. Although, these findings suggest CT scan to be an effective identification method of SARS-CoV-2 but it also has few disadvantages i.e., incapability to discriminate between the abnormalities caused by pneumonia and other lung diseases and COVID-19 [85].

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4.3. Immune Reaction-based Test Kits

In addition to the above described techniques, antigen-antibody (Ag-Ab) immune-reaction based kits provide more cost-effective and rapid diagnosis method. A recent study has proposed a detection method with proven 88.66% sensitivity and 90.63% specificity in laboratory experiment. The technique utilizes immune reaction of combined human antibodies i.e., immunoglobulin M (IgM) and IgG with SARS-CoV-2 coronavirus spike proteins from the blood sample of COVID-19 patient. This technique also showed consistent result for serum and plasma from venous blood and fingerstick blood sample [86]. Enzyme-linked immunosorbent assay (ELISA) based on the immune reaction can also be used for the detection of SARS-CoV-2. A study has suggested that the ELISA technique is capable of detecting the virus using recombinant nucleocapsid and spike viral proteins with positive rates of 80.4% and 82.2%, respectively. However, the positive rate of the experiment was less (60%) during the initial stage (0 to 10 days) of the infection which might be due to the low concentration of antibodies in blood sample [87]. Thus, these techniques could involve false negative results in some cases.

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Diagnosis Methods	Mechanism of Detection	Specimen	Advantages	Disadvantages	References
RT-qPCR	Polymerase chain reaction / hybridization reaction, electrophoretic separation	Respiratory samples, oropharyngeal swab, saliva	Specific and sensitive	Laborious, time consuming, hazardous, labor extensive, costly	[75]-[78]
CT Scan	X ray beam imaging of chest of patient, inspection of lung abnormalities	NA	Effective, specific, Non-hazardous, non-laborious	Incapable of discriminating different lung abnormalities, costly	[79]-[85]
Testing Kits/ ELISA	Antigen-antibody reaction, colorimetric interpretation	Blood, serum, plasma	Rapid, sensitive, cost-effective	Might be incapable of detection during initial stage of infection	[86]-[87]

Table 02: Different diagnosis methods for the detection of SARS-CoV-2. NA: Not Allowed.

5. Major Drug Targets against SARS-CoV-2

Different proteins involved in different stage of vial life cycle of SARS-CoV-2 can serve as potential therapeutic targets for designing antiviral drugs (**Table 03**). The best possible therapeutic options for SARS-CoV-2 are 3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase, structural proteins i.e., spike glycoprotein. These proteins are essential for the maintenance of the virus life cycle and hence recognized as most attractive drug targets against SARS-CoV-2 [88]. Analysis of the genome sequences of the catalytic sites and key-drug binding sites of these enzymes suggest high degrees of sequence similarity with those from SARS and MERS coronaviruses. And thus, the known inhibitors of these enzymes from SARS and MERS coronaviruses could be repurposed for the possible treatments of COVID-19 [89].

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Among these, the Spike protein of the coronavirus attaches to the angiotensin-converting enzyme 2 (ACE2) host receptor which facilitates the viral fusion and entry inside the host cell. So, the blocking of the interaction of the spike protein with the ACE2 receptor with specific inhibitor provides a strategy for potential antiviral development [90].

Both 3-chymotrypsin-like protease ($3CL^{pro}$) and papain-like protease (PL^{pro}) cleavesthe initially synthesized polyprotein complex required for the replication and transcription of the viral RNA [91].

The helicase of coronavirus possesses nucleotide-triphosphatase, duplex RNA/DNA-unwinding and RNA-capping activities that are essential for viral replication and proliferation and thus this enzyme is another attractive target for antiviral drug development against SARS-CoV-2 [92].

Coronavirus RNA-dependent RNA polymerase (RdRp) plays pivotal role in the viral replication and production of multiple copies of the viral genome. It also transcribes the subgenomic RNAs and mRNAs being located in the replicase complex [93].

Beside these, host cell membrane receptor protein and proteases i.e., ACE2 and TMPRSS2 have been proposed as the potential therapeutic targets against SARS-CoV-2 in few studies as these proteins are involved in ensuring the viral entry inside the host cell [94][95].

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Target Name	Target Category	Target Type	Function	References
Spike protein	Membrane protein	Structural viral protein	Attachment to host cell membrane and fusion inside the cell.	[90]
3-chymotrypsin-like protease ($3CL^{pro}$)	Enzyme	Non-structural viral protein	Cleavage of polyprotein complex required for viral replication and transcription.	[91]
Papain-like protease (PL^{pro})	Enzyme	Non-structural viral protein	Cleavage of polyprotein complex required for viral replication and transcription.	[91]
Helicase	Enzyme	Non-structural viral protein	Nucleotide-triphosphatase, duplex RNA/DNA-unwinding and RNA-capping	[92]
RNA-dependent RNA polymerase (RdRp)	Enzyme	Non-structural viral protein	Replication and transcription of viral RNA and mRNA.	[93]
Angiotensin converting enzyme 2 (Ace2)	Receptor	Host protein	Recognition and interaction with viral spike protein to assist viral entry.	[94][95]
Transmembrane protease serine 2 (TMPRSS2)	Enzyme	Host protein	Proteolytic cleavage to prime the spike protein-Ace2 receptor interaction in viral fusion	[49][94][95]

Table 03: Summary of different possible drug targets against SARS-CoV-2.

6. Therapeutic Options for COVID-19 Treatment

6.1. Antiviral Drugs and Other Candidate Molecules

The development of drugs against SARS-CoV-2 has become an urgent necessity to combat the COVID-19 pandemic. With about 15% of COVID-19 patients suffering from severe disease and hospitals being overwhelmed, treatments are desperately needed in this situation.Although, there is no specific drug or vaccine available which can be used to treat the COVID-19till now, ranges of non-specific drug have been proven effective to alleviate the COVID-19 condition [96].

A recent study has been carried on five FDA-approved drugs and two broad spectrum antiviral drugs to assess their inhibitory activities on SARS-CoV-2. Among these, Ribavirin (half-

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maximal effective concentration (EC_{50}) = 109.50 μM), Penciclovir (EC_{50} = 95.96 μM) and Favipiravir (EC_{50} = 61.88 μM) were required at higher concentration to inhibit the virus. Nafamostat and Nitazoxanide were required at comparatively lower concentration with EC_{50} values of 22.50 μM and EC_{50} = 2.12 μM but two compounds;Remdesivir (EC_{50} = 0.77 μM) and Chloroquine (EC_{50} = 1.13 μM) potently blocked virus infection at low-micromolar concentration (**Table 04**) [97].

Remdesivir was also shown to be effective in alleviating the COVID-19 condition of first infected person in USA and this drug is now on its phase III clinical trial on a check for COVID-19 treatment in China. A derivative of Chloroquine, Hydroxychloroquine is less toxic and shown to have comparable inhibitory effect as with Chloroquine and several trials on Hydroxychloroquine for COVID-19 treatment was initiated in China in February 2020 [98][99].

In yet another laboratory experiment, Remdesivir was shown to inhibit SARS-CoV-2 replication in Vero-E6 cells with EC_{50} at 23.15 μM. Moreover, Lopinavir, Homoharringtonine and Emetine were also shown to block the SARS-CoV-2 replication at EC_{50} values of 26.63, 2.55 and 0.46 μM, respectively in the same experiment [100]. Ivermectin, another FDA-approved drug is capable to inhibit the SARS-CoV-2 viral replication effectively [101]. Another recent study has shown that the ribonucleoside analog β-D-N^4-hydroxycytidine has antiviral activity not only against SARS-CoV-2 but also on other multiple bat coronaviruses including SARS and MERS coronaviruses. This analog is orally bioavailable and has increased potency against a coronavirus bearing resistance mutations to the nucleoside analog inhibitor Remdesivir [102].

SARS-CoV-2 infection of lung cells depends on cell membrane protease and Camostat mesylate, an inhibitor of TMPRSS2, blocks SARS-CoV-2 infection of lung cells. This inhibitor is also effective to inhibit the SARS and MERS coronavirus entry inside the lung cell [103]. A clinical

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study suggested that the combination of Lopinavir and Ritonavir showed notable therapeutic benefits to COVID-19 patients compared to using pneumonia-associated adjuvant drug alone [104]. These two drugs are also being tested in clinical trials now although, another clinical experiment claimed that no benefits were observed in hospitalized COVID-19 patient beyond the standard care using the combined medication [105][106]. On March 20, 2020, World Health Organization (WHO) launched megatrials on four most promising drugs i.e., Chloroquine, Hydroxychloroquine, Remdesivir, and combination of Ritonavir and Lopinavir and the combination plus IFN-β [107].

Drug Name	Category	Mechanism of Action on Viruses	Effects on SARS-CoV-2	Evidence on SARS-CoV-2	References
Ribavirin	Nucleoside analog, Antiviral (Approved)	Termination of viral mRNA synthesis.	Inhibits the virus with EC50 value of 109.50 μM.	*In vitro* experiment	[97]
Penciclovir	Nucleoside analog, Antiviral (Approved)	Interferes with viral replication and transcription.	Inhibits the virus with EC50 value of 95.96 μM.	*In vitro* experiment	[97]
Favipiravir	Antiviral, modified pyrazine analog (Approved, Investigational)	Interferes with replication and transcription by targeting RNA-dependent RNA polymerase.	Inhibits the virus with EC50 value of 61.88 μM.	*In vitro* experiment	[97]
Nafamostat	Serine protease inhibitor (Investigational)	-	Inhibits the virus with EC50 value of 22.50 μM.	*In vitro* experiment	[97]
Nitazoxanide	Antiprotozoal agent (Approved, Investigational)	Inhibits the replication of several RNA and DNA viruses.	Inhibits the virus with EC50 value of 2.12 μM.	*In vitro* experiment	[97]
Remdesivir	Antiviral, Nucleoside analog (Investigational)	Transcription termination by inhibiting the activity of RNA polymerase.	Inhibits the virus with EC50 value of 0.77 μM.	*In vitro* and clinical experiment (Under trial)	[97]-[99]
Chloroquine	Antimalarial drug, (Approved, Investigational)	Inhibits the terminal glycosylation of Ace2 receptor.	Inhibits the virus with EC50 value of 1.13 μM.	*In vitro* experiment.	[97]
Hydroxychloroquine	Antimalarial drug, (Approved)	Inhibits the terminal glycosylation of Ace2 receptor	Inhibits the virus effectively	*In vitro* and clinical experiment (Under trial)	[98][99]
Lopinavir	Antiretroviral protease inhibitor (Approved)	Interferes with the viral protease and results in the production of immature and non-infectious viral particles	Blocks the SARS-CoV-2 replication at EC_{50} value of 26.63μM.	*In vitro* and clinical experiment (Under trial)	[100]
Homoharringtonine	Protein synthesis inhibitor (Approved, Investigational)	-	Blocks the SARS-CoV-2 replication at EC_{50} value of 2.55 μM.	*In vitro* experiment.	[100]
Emetine	(Experimental)	-	Blocks the SARS-CoV-2 replication at EC_{50} value of 0.46 μM.	*In vitro* experiment.	[100]
Ivermectin	Anti-parasitic drug (Approved,	-	Blocks viral replication effectively.	*In vitro* experiment.	[100]

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	Investigational)				
β-D-N^4-hydroxycytidine	Antiviral, Nucleoside analog (Experimental)	Induces mutation on RNA viruses.	Inhibits multiple bat coronaviruses including SARS-CoV-2, SARS-CoV and MERS-CoV.	*In vitro* experiment.	[101]
Camostat mesylate	(Experimental)	-	Blocks TMPRSS2 and prevents viral entry inside cell.	*In vitro* experiment.	[102]
Ritonavir	Antiviral, protease inhibitor (Approved, Investigational)	Inhibits the viral replication.	Alleviates the COVID-19 condition in combination with Lopinavir.	*In vitro* and clinical experiment (Under trial)	[103][104][107]

Table 04: Different drugs that were found to act against SARS-CoV-2 in different laboratory and clinical experiments. General information was retrieved from DrugBank [108].

6.2. Repurposing Options of Drugs and Other Candidates for SARS-CoV-2

Drug repurposing is an effective drug discovery strategy from existing drugs, which could shorten the time and reduce the cost compared to de novo drug discovery.Since, different structural proteins and overall genome sequences of all three SARS-related coronaviruses have significant similarities and hence, it is logical that the drugs which work on previous two SARS-related coronaviruses might work on novel coronavirus as well [109].

For example, a potent MERS-CoV inhibitor, Nafamostat has recently been proven to also act against SARS-CoV-2. And thus, SARS-CoV $3CL^{pro}$ inhibitor i.e., 3-isotheaflavin-3-gallate (IC50 = 7 μM) is also expected to inhibit SARS-CoV-2 $3CL^{pro}$ [97][110]. In another distinct experiment, different keto-glutamine analogs were proven to inhibit SARS-CoV $3CL^{pro}$ [111]. Another laboratory experiment on a series of flavonoid derivatives showed different Biflavonoids can have potential inhibitory effects on $3CL^{pro}$ of SARS-Cov-2. Among different Biflavonoids, Amentoflavone was reported to have better $3CL^{pro}$ inhibitory activity with IC_{50} value of 8.3 μM [112].

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Helicase is the enzyme responsible for the unwinding of double stranded nucleic acid complex during replication and the inhibition of this enzyme prevents the viral reproduction cycle. Bannanin and its different derivatives (Iodobananin, Vanillinbananin and Eubananin) can effectively inhibit the SARS-CoV helicase activity [113]. Nucleoside analogs incorporate inside the extending DNA strand during the replication and terminates the replication process and thus inhibits the viral replication cycle. A nucleoside analog, β-D-N^4-hydroxycytidine was shown to inhibit the SARS-CoV viral replication with an approximatedEC_{50} of 10 μM in a laboratory experiment [114].

PL^{pro} is an enzyme which cleaves the initial polyprotein complex is a potential drug target for SARS-CoV-2. Different Tomentin derivatives were shown to inhibit the PL^{pro} enzyme with IC_{50} value ranging between 5.0 and 14.4 μM [115].

6.3. Therapeutic Monoclonal Antibody Preparation

Native virions present the most poten immunogen or antigen to be used in immunization or monoclonal antibody preparation [116]. Coronavirus spike protein is the most antigenic protein which interacts with ACE2 receptor and this interaction mediates the viral entry inside the host cell as mentioned earlier. Monoclonal antibodies (mAbs) provide excellent therapeutic option to prevent the SARS-CoV viral entry inside the host cell by interfering with the ACE2-Spike protein interaction [117].

A SARS-CoV-specific human monoclonal antibody, CR3022, has been proven to bind the receptor binding domain (RBD) of SARS-CoV-2 spike protein in a recent laboratory experiment. This finding suggests that CR3022 alone or in combination with other antibodies could be potential therapeutic option for COVID-19 treatment [118]. F26G18 and F26G19 are two

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different antibodies which can effectively bind with RBD of SARS-CoV spike protein *in vitro* [119]. However, the RBD shows high rates of mutations and therefore, might escape the mAbs-mediated neutralization in some cases. Therefore, other antibodies which are specific todomains except RBD i.e., two conserved heptad repeats (i.e. HR1 and HR2) of Spike protein can provide better therapeutic benefits [120]. Moreover, S230 is another monoclonalantibody which has recently been shown to block the SARS-CoV viral entry inside the cell by blocking the interaction with S1 subunit of spike protein with the cell membrane receptor ACE2 [121].

Beside these, immune sera from convalescent patients have been shown to be effective in the treatment of patients infected with SARS-CoV-2 making passive immune therapy with human monoclonal antibodies an attractive treatment option for COVID-19. So, the simplest and most direct way based on mAbs therapeutic interventions to treat the COVID-19 patientwould be to use the plasma from convalescent patients [122]. Thus, different mAbs could be used to alleviate the COVID-19 condition.

6.4. Therapeutic Intervention with Interferon

Recombinant human interferons were shown to be effective in treating SARS-CoV patient immediately after the SARS-CoV outbreak. IFN-β was shown to be more effective in a laboratory experiment followed by IFN-γ and interferon IFN-α in inhibiting viral replication in different cell lines [123]. In yet another *in vitro*study, IFN-β 1a was proven to inhibit the SARS-CoV replication in Vero E-6 cell line [124].

Falzarano et al. reported the efficacy of a combination containing IFN-α2β and Ribavirin on a novel β coronavirus, nCoV, as the causative agent of severe respiratory illness in humans originating in Saudi Arabia, Qatar and Jordan. They found both interferon-α2b and Ribavirin

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alone and the combination is effective against nCoV. However, the combination of interferon-α2b and Ribavirin together showed slightly better effect [125]. Conversely, SARS-CoV ORF 3b, ORF 6, and nucleocapsid proteins were reported to inhibit a key protein required to express IFN-β, IFN regulatory factor 3 (IRF-3) in host cell in a distinct *in vitro* study [126].

A recent study has suggested interferon β as the most suited option for the treatment of COVID-19 and also SARS-CoV-2 might have more sensitivity towards IFN than other SARS-related coronaviruses [127]. Another *in vitro* study about the effects of interferon on SARS-CoV and SARS-CoV-2 has found that the pretreatment of viral infected cells with type I interferon (IFN-I) resulted in much higher decrease in SARS-CoV-2 virus titer than that of SARS-CoV titer in 48 hours. A deficit in the viral nucleocapsid protein was observed after the treatment with IFN-I. The experiment also suggested that SARS-CoV-2 might be more sensitive to IFN-Itreatment and this is might be due to the change in viral protein [128].

6.5. RNA Interference

RNA interference (RNAi) is a conserved biological response to double stranded RNA that is commonly used in post-transcriptional gene silencing [129]. This technique utilizes 19-23 base pair double-stranded RNA to degrade targeted RNA in a specific and stepwise manner [130]. RNAi is commonly used to generate gene-knockouts and study gene function in different organisms. RNAi assisted inhibition of replication has been reported in many viruses including those that infect human in different studies [131].

RNAi technique was also studied extensively to inhibit different viral proteins of SARS-CoV in different laboratory experiments. It is capable of inhibiting the SARS-CoV spike protein encoding gene expression in HEK 293T cells as proven in *in vitro* experiment [132]. In another

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distinct laboratory experiment, designed small interfering RNA (siRNA) was directed against three subgenome RNA of SARS-CoV. Significant reduction in the expression of the targeted RNAs was observed without interfering the expression of other RNAs [133]. The SARS-CoV viral replication can be effectively reduced as evident with 85-90% reduction in viral genome RNA using siRNA-based RNAi technology in vero E6 cells in laboratory experiment [134].

Moreover, a previous study carried out on animal model using rhesus macaque (*Macaca mulatta*) showed significant improvement in SARS-severity in the subject animals rather than the controls upon siRNA-based therapy [135].

6.6. Vaccine

Vaccination is one of the most efficient ways to prevent viral diseases. A vaccine helps the body's immune system to recognize and fight pathogens like viruses or bacteria, which then keeps us safe from the diseases they cause [136]. With no specific antiviral drug and specific vaccine for COVID-19, the development of such one is urgently required but it would take a significant period of time. Moreover, there are significant hurdles to overcome during the development of vaccine against SARS-CoV i.e., immunopotentiation in the form of eosinophilic infiltration or increased infectivity, target population on which the vaccine will work and the mutation rate of the virus.

There are different types of vaccines i.e., live vaccines, attenuated vaccines, Inactivated/killed vaccines, Subunit and conjugate vaccines, Toxoid vaccines [137]. In the case of COVID-19, 79 vaccine candidates are in active development (confirmed as of early April 2020), 74 were not yet in human evaluation with only five in phase I clinical trial.

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As reported by Coalition for Epidemic Preparedness Innovations (CEPI) scientists in April, 2020, 115 total vaccine candidates are in early stages of development, with 78 confirmed as active projects (79, according to the Milken Institute), and 37 others announced, but with little public information available (presumed to be in planning or being designed) [138][139].

In April after the CEPI report was published, Phase I-II randomized, interventional trials for dosing and assessment for side effects began in Wuhan, China on the candidate vaccine, Ad5-nCoV (CanSino Biologics) [140], and in England on the candidate, ChAdOx1 nCoV-19 [141]. **Table 05** and **06** enlist most updated information about the vaccine development progresses in clinical and preclinical phases in different companies and industries.

Phase I trials test primarily for safety and preliminary dosing in a few dozen healthy subjects, while Phase II trials, following success in Phase I, evaluate effective dose levels and side effects of the candidate vaccine in dozens-to-hundreds of people either with the targeted disease or in healthy subjects. A Phase I-II trial conducts preliminary safety and dosing testing, is typically randomized, placebo-controlled, and at multiple sites, while determining more precise, effective doses [142]. Therefore, due to the extended period of clinical phases and additional manufacturing steps, it will certainly take a while for the vaccines to be available in the market.

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Candidate	Characteristics	Developer	Status	Same Platform for non-coronavirus Candidate	Reference
Ad5-nCoV	Adenovirus type 5 vector expressing S protein	CanSino Biologics	Phase-1 (NCT04313127) Phase-2 (NCT04341389)	Ebola	[143] – [146]
ChAdOx1 nCoV-19	An attenuated adenovirus capable of producing the S protein of SARS-CoV-2 that permits for the formation of endogenous antibodies against these proteins	University of Oxford	Phase-1 (NCT04324606)	MERS, Influenza, TB, Chikungunya, Zika, MenB, Plague	[143][147] [148]
mRNA-1273	LNP-encapsulated mRNA vaccine that encodes S protein	Moderna	Phase-1 (NCT04283461)	Multiple Candidates	[143][149] [150]
Covid-19/aAPC	aAPCs modified with lentiviral vector which expresses synthetic minigene based on domains of selected viral proteins	Shenzhen Geno-Immune Medical Institute	Phase-1 (NCT04299724)	-	[151]
LV-SMENP-DC	DCs modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins and directed with antigen-specific CTLs	Shenzhen Geno-Immune Medical Institute	Phase-1 (NCT04276896)	-	[152]
INO-4800	Electroporation delievers DNA plasmid encoding S protein	Inovio Pharmaceuticals	Phase-1 (NCT04336410)	Lassa, Nipah,HIV, Filovirus, HPV, Cancer indications, Zika, Hepatitis B	[143][153] [154]

Table 05: Vaccine candidates under clinical trial for COVID-19.

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Candidate Type	Platform	Developer	Current Status	Same platform for non-coronavirus candidates	Reference
DNA with electroporation	DNA	Karolinska Institute / Cobra Biologics (OPENCORONA Project)	Pre-Clinical	-	[155] - [157]
DNA plasmid Vaccine	DNA	Zydus Cadila	Pre-Clinical		[158][159]
adenovirus-based NasoVAX expressing SARS2-CoV spike protein	Non-Replicating Viral Vector	Altimmune	Pre-Clinical	Influenza	[160] – [163]
DNA plasmid Vaccine	DNA	Osaka University/ AnGes/ Takara Bio	Pre-Clinical	-	[164][165]
S protein (baculovirus production)	Protein Subunit	Sanofi Pasteur	Pre-Clinical	Influenza, SARS-CoV	[166]
LNP-encapsulated mRNA encoding RBD	RNA	Fudan University/ Shanghai JiaoTong University/RNACure Biopharma	Pre-Clinical	-	[167]
Measles Vector	Replicating Viral Vector	Institute Pasteur/Themis/Univ. of Pittsburg Center for Vaccine Research	Pre-Clinical	West nile, chik, Ebola, Lassa, Zika	[168][169]
Recombinant protein, nanoparticles (based on S-protein and other epitopes)	Protein Subunit	Saint-Petersburg scientific research institute of vaccines and serums	Pre-Clinical	-	[170] – [172]
MVA expressing structural proteins	Non-Replicating Viral Vector	Centro Nacional Biotecnología (CNB-CSIC), Spain	Pre-Clinical	HIV, HCV, chikungunya, Ebola, zika, malaria, leishmania	[173]
Plasmid DNA, Needle-Free Delivery	DNA	Immunomic Therapeutics, Inc./EpiVax, Inc./PharmaJet, Inc.	Pre-Clinical	SARS	[174][175]

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Table 06: Selected vaccine candidates under preclinical research for COVID-19

7. Concluding Remarks

After transmission to human body the virus fist enters the targeted cells of host where they carry out replication and produce multiple copies of the virus. Then newly assembled virions then lyse the host cells and continue to infect new healthy cells which characterize the pathogenesis. The knowledge of pathogenesis may help to understand the necessity of preventive measures, basis of diagnosis and possible therapeutic options. Early diagnosis of the infected patient and isolation is a prerequisite to combat the outbreak of any contagious viral pathogen. Diagnosis of the SARS-CoV-2 virus can be achieved in variety of means which vary depending on the types of samples used and involve ranges of advantages and disadvantages. Although, no specific therapeutic option is currently available which can be used to effective treat COVID-19, many approaches have been taken recently and few of those are under clinical trial now. Different candidate molecules, drugs and other preparations have already shown positive responses against SARS-CoV-2 but these are not clinically proven and hence need further evaluation. Of course, a definitive cure which can help patients recover will be available soon.

Conflict of Interest

Authors declare no conflict of interest regarding the publication of the manuscript.

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