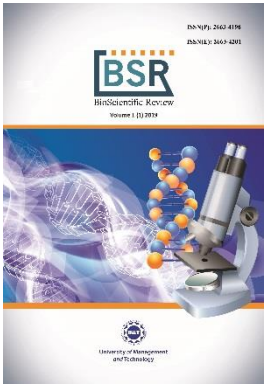

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Overview of Immune Perspectives and Current Treatment Strategies against COVID-19

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Abstract

COVID-19 is a highly infectious respiratory disorder, affecting millions with about 10% fatality rate. Infected patients may be symptomatic and show mild to severe symptoms, manifesting as mild fever, cough, headache, and nausea or they may remain asymptomatic, showing no symptoms at all. World Health Organization (WHO) reported over 260, 493 573confirmed cases worldwide with 5 195, 354deaths (November 2021). There are myriads of promising approaches to pharmacologically treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the newly reported seventh human coronavirus responsible for the COVID-19 pandemic. There are various types of potential drugs, such as monoclonal antibodies, interferon therapies, peptides, small molecule drugs, oligonucleotides, and vaccines, under consideration to target various structural components of the virus. This study focused on reviewing potential drug candidates, namely remdesivir, lopinavir, emetine, aloxistatin, viracept, homoharringtonine, ivermectin, favipiravir, tocilizumab, chloroquine, and leronlimab that can be used to treat COVID-19 infection. These drugs target the membrane nucleocapsid, spike, or envelope proteins, and are either in clinical trials or are under consideration. These drugs directly inhibit the viral infection, while others trigger the immune system to fight against the virus. We also overviewed the immunization ability of in-use and accepted vaccines, such as Pfizer and Moderna. It was followed by a review of research dealing with the immune system and how it tries to manage the infection as well as vaccines and potential therapeutic agents.

1. Introduction

Coronaviruses (CoVs), the largest RNA enveloped viruses having crown-like spikes, belong to the *Coronaviridae* family [1]. They are important human pathogens. To date, six coronaviruses have been reported to cause respiratory diseases, including common cold CoVs (NL63, OC43, HKU1 and 229E) and highly pathogenic CoVs (MERS-CoV and SARS-CoV) [2]. Previously, two major epidemics of human coronavirus (HCoV) were

reported including severe acute respiratory syndrome (SARS) in 2002, having a 10% fatality rate [3] and Middle East respiratory syndrome (MERS) in 2012, having a 39% fatality rate [4]. The novel coronavirus, severe acute respiratory coronavirus 2 (SARS-CoV-2), originated in Wuhan, China [5] and was found to be the cause of COVID-19 pandemic. This infection is a respiratory syndrome of the lower respiratory tract. It is characterized by dry cough, fever, tiredness, sore throat, nausea, and less frequently, diarrhoea [6]. Clinically, pneumonia is the preliminary feature; however, RNAemia and acute respiratory distress syndrome (ARDS) are also observed in critical patients.

COVID-19 outbreak was massive and spread all over the globe at an alarming rate. In February 2020, the World Health Organization (WHO) declared it a public health emergency of international concern [7]. WHO reported 245,373,039 confirmed cases with 4,979,421 deaths till October 2021[8]. The incidence of acquiring the disease directly correlates with age and associated comorbidities such as obesity, diabetes mellitus, cardiovascular diseases, hypertension, a pulmonary disorder, or renal disease [9]. The percentage of mortality for younger individuals with this disease is approximately 7% and 55% for patients older than 60 years [10, 11]. A study comprising 140 COVID-19 patients reported approximately equal chances (1:1 ratio) of disease in males and females [12]. The following review summarizes the structural features, immune perspective, and potential treatment strategies against SARS-CoV-2. It also reviews the topical status of vaccination against this ailment.

2. SARS-CoV-2; Etiology, Genomics, and Morphology

After entry, the incubation period for SARS-CoV-2 ranges between 5 to 7 days. However, 14 days were also reported in some patients [13]. COVID-19 cases could be categorized into mild, moderate, severe or critical. The majority of COVID-19 patients (81%) represented mild symptoms, such as mild fever, sore throat, nasal congestion, muscle ache and malaise without radiographic features. Moderate cases of COVID-19 mostly display symptoms such as tachypnea and shortness of breath, while severe cases exhibit sepsis and respiratory distress syndrome (ARDS), which is also a leading cause of mortality [14]. COVID-19 patients having critical conditions have shown respiratory failure, cardiac injury, RNAemia, septic shock, or multiple organ dysfunction [15, 16].

Elevated prothrombin time, creatine kinase, C-reactive protein (CRP), D-dimer, and ALT with lymphopenia (CD4 and CD8) [15] commonly occur in COVID-19 sufferers. Severe cases of COVID-19 exhibit high leucocyte and neutrophil-lymphocyte ratio (NLR) with a lower percentage of basophils, eosinophils, and monocytes [17]. Furthermore, COVID-19 patients in the intensive care unit (ICU) exhibit markedly increased profile of interleukin (IL)-6, IL-2, IL-10, IL-8 (chemokine), interferon gamma-induced protein 10 (IP10), granulocyte colony-stimulating factor (GCSF), monocyte chemotactic protein 1 (MCP1), macrophages inflammatory protein alpha (MIP1A), and tumor necrosis factor (TNF)-α [2, 18]. On the other hand, COVID-19 non-survivors have shown elevated ferritin, IL-6, neutrophil count, blood urea, D-

dimer, and creatinine phosphate [19, 20]. Anti-52 kDa S6SA/Ro antibody, anti-60 kDa SSA/Ro antibody, and antinuclear antibodies were also found prevalent in patients. Ground-glass opacity and bilateral patchy shadowing on chest CT-scan are other important clinical findings [21].

SARS-CoV-2 contains the largest positive-sense RNA genome ranging between 26 to 32kb with a 5'-methyl cap and 3'poly-A tail [22]. The full-length genome sequencing of SARS-CoV-2 revealed 88.99% [23] and 79.5% sequence similarity with SARS-like coronaviruses and SARS-CoV, respectively [24]. The genome of the mature virus is associated with phosphorylated nucleocapsid (N) protein and is encased in phospholipid bilayer envelope with embedded spike glycoprotein trimmer (S), hemagglutinin-esterase, membrane (M) protein, and envelope (E) protein as shown in Figure 1 [1]. Among these, E protein increases the pathogenicity since it is involved in the assembly and release of viruses [25]. Besides these structural proteins, different CoVs also synthesize other structural proteins such as HE protein, 3a/b protein, and 4a/b protein [26].

S protein homotrimers make up the spikes of SARS-CoV-2 which binds with the angiotensin-converting enzyme (ACE)-2 receptors for host cell entry [20]. Afterwards, conformational changes in S protein promote the fusion of the viral envelope with the host cell membrane. The virus inoculates its RNA genome into the cell where it is translated into polyproteins as shown in Figure 2. Viral proteinases break down the polyproteins into smaller protein products. During discontinuous transcription, genomic mRNAs are produced and translated into viral proteins. Genomic RNA and viral polyproteins are assembled in the endoplasmic reticulum (ER) and Golgi apparatus, from where they are released in the extracellular milieu [6].

It has also been observed that infection due to SARS-CoV-2 primarily begins when its spike S protein binds to the entry receptors of the cells, whose tissue distribution and expression impacts the viral pathogenicity and tropism. noteable examples include angiotensin-converting enzyme 2 (ACE2; SARS-CoV, SARS-CoV-2 and HCoV-NL63),

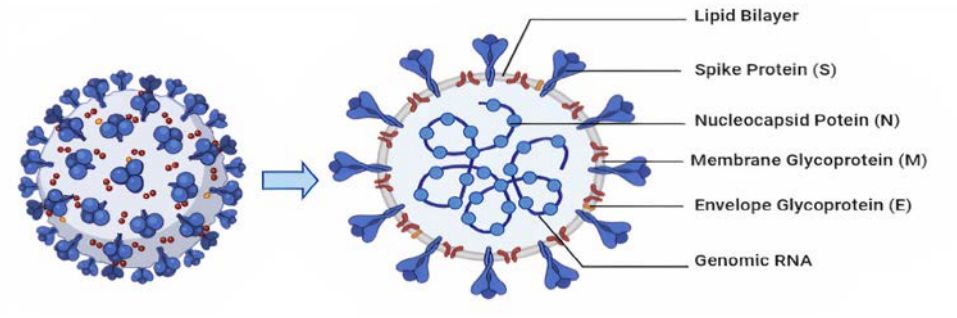

Figure 1. Structure of SARS-CoV-2. The structure is comprised of positive-sense ssRNA encased in the lipid bilayer, having four structural proteins including S-E-M-N.

aminopeptidase N (APN; HCoV-229E), and dipeptidyl peptidase 4 (DPP4; MERS-CoV).

Moreover, to enhance the therapeutic and prophylactic activities against COVID-19, a deeper understanding of the pathobiology of the virus is of immense importance. As mentioned above, receptor binding domain (RBD) of spike (S) protein is used by the SARS-CoV-2 to bind with ACE2 of the host to enter into the human cell [27]. The structural homology and highly genomic similarity between the S proteins of SARS-CoV-2 and previously known SARS-CoV helped locate the contact residues that interact with ACE2. The contact residues It weresimilar to SARS-CoV and was also found to be conserved not only in SARS-CoV-2 but also in other members of SARS-CoV species [28]**.** Apart from this, virus S protein priming requires the cellular transmembrane serine protease2 (TMPRSS2) that is expressed in the respiratory tract of humans. It dominantly assists in the entry of pathogens such as SARS-CoV. Non-essentially, the entry can also be assisted using lysosomal/endosomal cysteine proteases cathepsin L and B (CTSL, CTSB). Moreover, in vitro analysis revealed that hindrance of all three proteases inhibits the entry of SARS-CoV, while in the case of SARS-CoV-2, suppression of TMPRSS2 was sufficient to prevent its entry into primary lung cells and lung cell lines [28].

More recently, a distinct feature of S protein of SARS-CoV-2 was identified by identifying presence of polybasic cleavage site (PRRAR) at the S1-S2 boundary. This acquisition is efficiently cleaved by the prototype proprotein convertase furin that overcomes the species barrier and causes successful infection. This may also enhance the transmissibility, the expansion of zoonotic potential and cell tropism of SARS-CoV-2 [28]**.** After attachment and entry into the host cell, SARS-CoV-2 begins the translation of the replicase gene. For the cleavage of replicase polyproteins, the virus encodes a few proteases. To synthesize RNA, a suitable environment is generated by assembling myriads of non-structural proteins (nsps) (that consist of variable enzyme domains and functions) into the replicase-transcriptase complex (RTC) [29]**.** Furthermore, it was observed that there are still various accessory and non-structural proteins present in SARS-CoV-2 but their functions and characteristics are not fully known. The discovery of their activity will improve the therapeutic targets, which will inhibit viral replication [29].

3. Immunology and Novel Coronavirus (SARS-CoV-2)

The immune system is a key player in combating coronavirus-related infections [1]. Recent studies have suggested that SARS-CoV-2 regulates both, humoral and cellular division of the immune system, suggesting that they possess a role in immune-mediated protection [30].

3.1. Innate Immune Response against SARS-CoV-2

At present, an assessment of immune response effectiveness against SARS-CoV-2 is not completely known. Interferon (IFN) type I, a component of innate division usually develops as an initial response against viral infections via controlling viral replication [31]. The response against a virus is initiated after a successful recognition of viral invasion. In the case of RNA viruses such as SARS-CoV-2, pathogen-associated

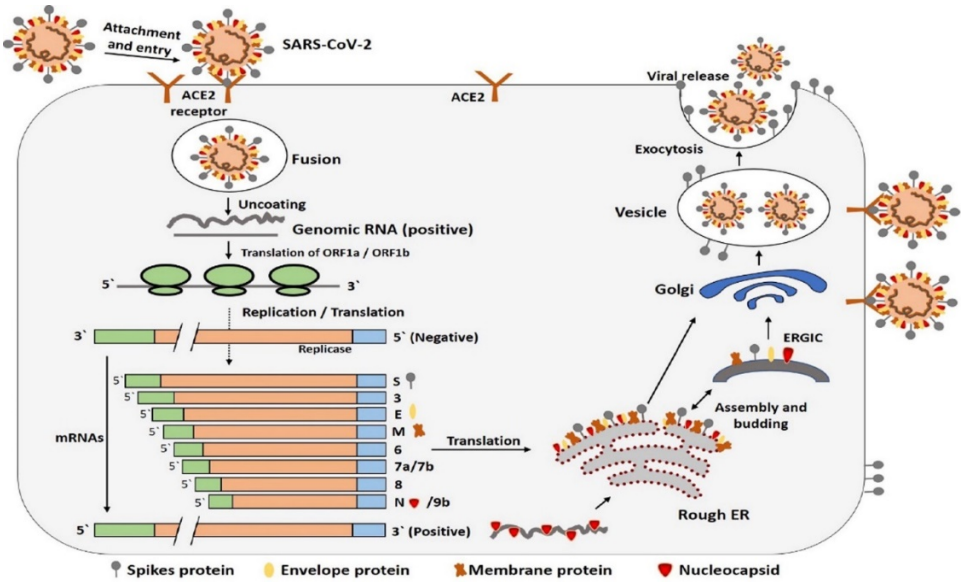

Figure 2. The Life Cycle of SARS-CoV-2**.** The life cycle of SARS-CoV-2 begins when S protein binds to the host cell receptor (ACE2). After that viral envelope fuses with the host cell membrane. Next, the virus releases its genomic RNA into the host cell where it is translated into polyproteins, which are then broken down into smaller protein products. During discontinuous transcription, sub-genomic mRNAs are produced by polymerases and then translated into viral proteins. In the Golgi apparatus and ER, genomic RNA and viral proteins are assembled into virions, which are then released out of the host cell. [6]

molecular patterns (PAMPS) are recognized by endosomal RNA receptors, toll-like receptors (TLR3 and TLR7), and cytosolic RNA receptors like RIG-I. TLRs are mainly involved in the recognition of lipids, lipoproteins, proteins, and nucleic acid of invading parasites at the cell membrane, endosomes, and lysosomes [32]. Immediately, after recognition, the oligomerization of receptors regulates the downstream signaling cascades, such as regulatory transcription factors, interferon regulatory factors (IRF3), and nuclear factors (NF)-kB [22]. This results in the expression of proinflammatory cytokines and type I IFN as the first line of defense. The main pattern recognition receptors (PRRs), activating the downstream pathways for the IFNs production, are TLRs, RIG-I-like receptors (RLRs) and NOD-like receptors (NLRs) [33]. In response, type I IFN activates the Janus kinase signal transducer and activator of transcription (JAK-STAT) signaling pathway. Afterwards, JAK1 and tyrosine kinase 2 (TYK2) phosphorylate the STAT1 and STAT2, which develops a complex with IRF9 to initiate the transcription of IFN stimulated gene (ISGs) [34]. The successful type I IFN ultimately suppresses the viral infection at an early stage as shown in Figure 3.

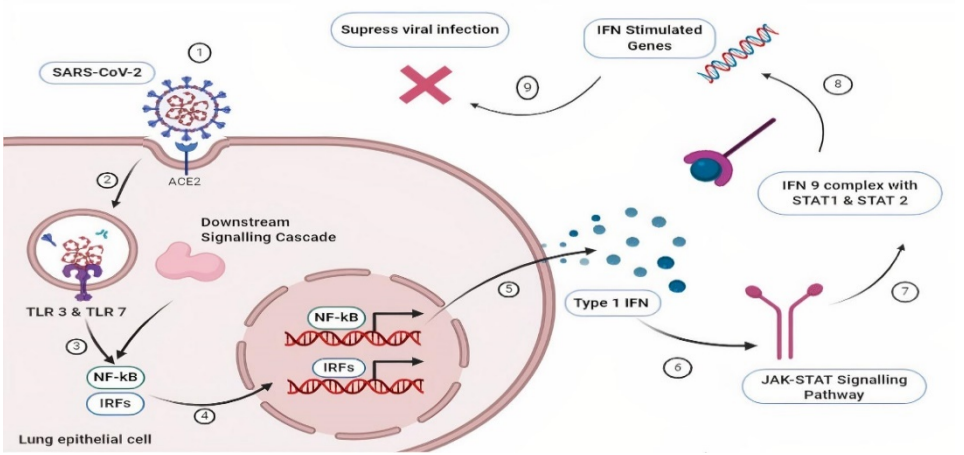

Figure 3. Host Innate Immune Response against SARS-CoV-2. Attachment of virus to the host cell is recognized by TLR3 and TLR7. After recognition, oligomerization of receptors regulates the downstream signalling cascades, such as NF-kb and T signalling pathways. Afterwards, JAK1 and TYK2 phosphorylate the STAT1 and STAT2, which results in the expression of type 1 IFN. In turn, type 1 IFN activates the JAK-STA and develops a complex with IRF9 to initiate the transcription of IFN stimulated genes (ISGs) that suppress the viral infection. The figure was made using BioRender (https://app.biorender.com/)

IFNs, the main immunomodulatory molecules, inhibit viral spread by activating macrophages, natural killer (NK) cells, and T and B lymphocytes. Structural and non-structural proteins of CoVs modulate IFN response to inhibit the signaling pathway [1]. The genomic similarity of SARS-CoV-2 with SARS-CoV and MERS-CoV reveals the possibility of a similar mechanism that can be used to modulate the type I IFN response to downregulate the innate immune response [31]. Therefore, their inhibition puts the host in imminent danger [35]. Various cell and animal models of SARS-CoV-2 infection exhibit a unique but inappropriate pattern of the inflammatory response which is characterized by the low level of type I and II IFNs. However, IL-6 and chemokines markedly increase. The significant reduction in innate antiviral response along with increased inflammatory cytokine production is the defining and deriving feature of COVID-19 [36].

Immunocompromised people, due to underlying morbidities, such as hypertension, cardiovascular disease, and diabetes mellitus, are more susceptible to infection [37]. A clear mechanism of the immune response against SARS-CoV-2 is yet to be investigated.

3.2. Adaptive Immune Response against SARS-CoV-2

T helper type 1 cells (Th1) play a critical role in the adaptive immune response against viral infections. Among these cells, $CD4^+$ T cells activate B cells for the immune response, while $CD8^+$ T cells exhibit cytotoxicity by killing virally

infected cells [38, 39]. Production of antibodies and humoral immune response play an important role in preventing the cells from reinfection in the future. In contrast to the humoral immune response, the cellular immune response is another mechanism of adaptive immunity. It can be seen inside the infected cells, which is mediated by the T-lymphocytes [40].

SARS-CoV-2 enters the host cell via the ACE2 cell receptor. Endosomal TLR7 senses the attachment of virus as shown in Figure 4 [41]. The activation of TLR7 leads to the production of α-IFN, TNFα, IL-6, and IL-12, which results in the activation of $CD8^+$ cytotoxic T cells and $CD4^+$ helper T cells. Then, these T cells produce antibodies and antigen-specific B cells as shown in Figure 4. This type of adaptive immunity plays a critical role in combating viral infection. In the case of immunocompromised patients, the body is unable to produce an adequate adaptive immune response against the virus, due to which severe symptoms occur and damage the body. The symptoms may lead to ARDS, cytokine storm, failure of body organs, and even death [42]. With age, the number of naïve T cells decreases, which means that the immune system's ability to react against the pathogen also decreases. In contrast, children have a huge population of naïve T cells ready to fight against viruses [43]. This can be the reason behind the prevalence of more severe cases of COVID-19 among elders.

For SARS-CoV, seroconversion was seen on the 4th day after the onset of the disease. Even 2 years after infection, neutralizing antibodies, and Immunoglobin G (IgG) were reported in [44]. In the case of MERS-CoV, seroconversion was observed after 2 to 3 weeks of the onset of disease [45]. The infected patients showed high production of Immunoglobin M (IgM) on the 9th day of infection, while on the 2nd week, Immunoglobin G (IgG) was at its peak [23]. In vitro studies have shown that all sera from the patients of COVID-19 were able to neutralize the novel coronavirus [46].

In the case of SARS-CoV, T cell response was highly investigated. According to a report, the response of $CD8^+$ T cells was highly observed against SARS-CoV, while the dominant response of Th1 cells was observed against MERS-CoV [47]. Furthermore, it was determined that neutrophils also have a destructive role against many infections, but their function remains unanswered in the case of human coronaviruses [31]. The current studies on coronaviruses showed that Th1 cell response is a key factor for successfully controlling SARS-CoV and MERS-CoV as well as SARS-CoV-2. Epitopes of B and T cells were extensively investigated for the structural proteins (S-E-M-N) of previously reported HCoVs [45]. If these epitopes can be identified in the case of SARS-CoV-2, it will help in creating passive immunity by using the serum from the recovered patients of COVID-19. It will also aid in making a more effective vaccine against the HCoVs as well as SARS-CoV-2 [31]. In this regard, a vaccine platform based on DNA was chosen due to its ability to instigate both the humoral and cellular immune response along with its quick design and manufacturing property. According to investigations, SARS-CoV-2 DNA vaccine candidates do not present the symptoms associated with vaccine-associated enhanced respiratory disease (VAERD) that is caused by Th2-bias vaccine modality since it urges a balanced Th1/Th2 response [48]

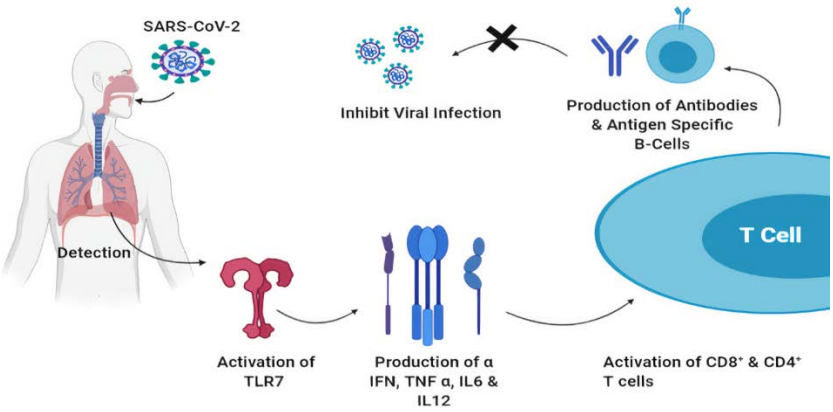

Figure.4 Host Adaptive Immune Response against SARS-CoV-2. SARS-CoV-2 enters the host cell and activates the endosomal TLR7, which results in the production of αIFN, TNFα, IL-6 and IL-12. In response, it activates the CD8+ and CD4+ T cells, leading to the production of antibodies and antigen-specific B cells that inhibit the viral infection.The figure was made using BioRender (https://app.biorender.com/)

4. Treatment Strategies

Contemporary analysis and research are continuously inaugurating various treatment strategies against SARS-CoV-2 [49]. At present, there is no single antiviral therapy for CoVs, only supportive treatments are available. According to physicians and guidelines of WHO, the suspected individual with COVID-19 should be quarantined in a room, while the confirmed cases should be isolated and cared for in the hospital or a room with personal protective equipment (PPE) [50]. Paracetamol and guaifenesin can be used as first-line treatments for fever and non-productive cough. Immunocompromised patients with other underlying diseases need to be hospitalized and should be treated with available drugs. Only a limited number of cases need to be admitted to ICU. These cases are often in a critical condition and have severe symptoms, such as shortness of breath [51]. They require immediate oxygen therapy to maintain the process of breathing.

Many drugs have proven to be effective against SARS-CoV and MERS-CoV. As SARS-CoV-2 is also a member of β-CoVs and has genomic similarity with SARS-CoV and MERS-CoV, there might still be a possibility that the same drugs could be effective against COVID-19. Remdesivir is an antiviral drug that was effective against SARS-CoV and MERS-CoV because it inhibits the transcription of viral RNA at an early stage [17]. Ribavirin is used against many viral infections including SARS and MERS since it inhibits the synthesis of viral RNA inside the host cell [52]. Griffithsin, a broad-spectrum antiviral agent, targets the spike protein to inhibit the attachment of the virus to the host cell [53]. It is highly effective against many viruses, including human CoVs. Rapamycin, Imatinib, and

Dasatinib are antiviral drugs used to block the entry of viruses by inhibiting the kinase signaling pathways [54].

IFNs are the cytokines of innate immune response and can be expressed by various cell types after a viral infection. After binding to specific cell surface receptors, they activate the antiviral pathways to limit the spread of the virus [55]. All HCoVs can reduce the response of IFNs. For this reason, the recombinant IFNs, such as α and β IFN, can be effective therapeutic agents against SARS-CoV-2, since they induce the innate immune response against many viruses, such as SARS-CoV [56, 57].

4.1. Direct Therapeutic Drugs against the Virus

Some of the reported therapeutic drugs directly inhibit the viral infection inside the body. They mainly inhibit viral replication and protein translation inside the host.

4.1.1. Remdesivir

An adenosine analog, such as HCoV-229E, SARS-CoV, MERS-CoV, and HCoV-OC43, was previously used against HCoVs [58, 59]. It inhibits viral replication at an early stage inside the host cell. The enzyme responsible for RNA replication from the RNA template is known as RNA-dependent RNA polymerase (RdRp). It is also recognized as nsp-12 and is an indispensable part of RNA viruses since it plays a crucial role in their life cycle [60]. In the case of SARS-CoV-1, nsp-7 and nsp-8 ensure the processivity of nsp-12 so it performs its RNA-synthesizing activity. This tripartite polymerase complex along with nsp-14 performs the proofreading exonuclease activity. It was found that the sequence of SARS CoV was 96% similar to SARS CoV-2 with respect to RdRp [61]. For this reason, agents targeting RdRp of SARS CoV are also expected to target RdRp of SARS CoV-2 [62]. A deeper analysis revealed that remdesivir (GS-5734) acts as an RNA-dependent RNA polymerase (RdRp) binding substrate and metabolizes into an adenosine nucleotide analog (GS-441524). It further phosphorylates and converts into a nucleoside triphosphate (NTP) and is taken as a substrate for SARS-CoV RdRp instead of ATP. Incorporation of these NTPs into viral replication machinery causes incompetent elongation. Hence, the substitution of ATP during polymerization causes chain termination without inhibiting the human mitochondrial RNA polymerases as well as human RNA Pol II [63]. Hence, due to the mechanism of action of remdesivir, the nucleoside analog prevents the replication of the viral genome by targeting the RdRp enzyme [62]**.** It was previously tested for the treatment of hemorrhagic fever caused by the Ebola virus, but it could not perform well during clinical trials [52, 64]. In December 2019, in vitro experiments were performed to check the efficacy of remdesivir against SARS-CoV-2. It was found that the drug reduced the viral infection. In January 2020, it was first used successfully against COVID-19 in affected patients [5]. It is currently in the fourth phase of clinical trials against COVID-19 [19]. It is found to be effective against SARS-CoV-2 since no side effects have been reported in patients.

4.1.2. Lopinavir

It is used with ritonavir and is known as an HIV protease inhibitor. It is also approved by FDA [65]. Proteases aid in viral replication since they can cleave both structural and functional proteins, enabling

the maturation of the virus. Lopinavir, a protease inhibitor, can effectively inhibit viral replication to limit the spread of the virus [11]. It was used to effectively treat SARS and MERS. However, when it was used along with ritonavir, it showed many side effects in patients. Lopinavir and ritonavir in combination with or without ribavirin are under clinical trials to treat COVID-19. According to another report, lopinavir without ribavirin was effective against SARS-CoV-2 during in vitro experiments [65].

4.1.3. Emetine

It is a protein synthesis inhibitor that has antiviral activity against many DNA and RNA viruses [66]. These include ebolavirus, rabies virus, zika virus, bovine herpesvirus 1, influenza virus, and buffalo poxvirus [67–71]. It effectively inhibits the replication of β-CoVs, such as HCoV-OC43, SARS-CoV, MERS-CoV, and HCoV-NL63 [72]. Currently, it is under clinical trials for the treatment of COVID-19 [65]. Its general mechanism of action includes the hindrance of ribosomal protein synthesis. Emetine was also identified to prevent the polypeptide bond incorporation by inhibiting the transfer reaction of aminoacyl-sRNA [63].

4.1.4. Aloxistatin (E-64D)

Aloxistatin (E-64D) is a cysteine protease inhibitor of cathepsins and calpains. It performs regulatory functions in cancer therapy and neurodegeneration. In the case of SARS-CoV-2, aloxistatin inhibits the viral entry by 92.3%, since cathepsin L is an obligatory factor for coronavirus cell entry. The structural investigation of the aloxistatin revealed its interaction with the main protein (Mpro) of SARS-CoV-2, which is dominant during the synthesis of nonstructural proteins (NSP). Hence, it is considered a promising drug candidate that could affect viral proteases [63].

4.1.5. Viracept (nelfinavir mesylate)

It is an anti-retroviral drug that is found to primarily inhibit HIV protease. Mechanistically, viracept targets the SARC-CoV-2 spike S glycoprotein and inhibits the S-o and S-n-mediated cell fusion. This indicates the drug's potential to prevent the viral spread and its transferability from one cell to another as well as its enhanced sensitivity towards neutralizing antibodies [63].

4.1.6. Homoharringtonine

It is an alkaloid derived from the plant *Cephalotoxus fortunei*. It has anti-tumor activity, which usually inhibits the viral protein translation. In the past years, it has been used against the herpes virus, rhabdovirus, murine hepatitis virus, coronaviruses, echovirus 1, and hepatitis B virus [67, 73]. By mechanism, HHT binds and interacts with the A-site of peptidyl transferase of the ribosomes and inhibits the translation of proteins [63]. Omacetaxine, a semi-synthetic homoharringtonine, is an FDA approved drug used for the treatment of chronic myeloid leukemia [74]. In vitro experiments showed that it is also effective in reducing the SARS-CoV-2 infection [65].

4.1.7. Ivermectin

This is an FDA-approved drug that is antiparasitic. It possesses the potential to be adopted as a drug against neglected topical diseases; however, it is still not approved for the treatment of any viral disease. The

proposed mechanism of action of ivermectin suggests the inhibition of a crucial intracellular transport procedure that is utilized by the virus to increase the infection through the suppression of the host's antiviral response, that is, inhibition of the host importin alpha/beta-1 nuclear transport proteins [75]. The analysis of nuclear transport inhibitory activity of ivermectin suggests that it is equally effective as SARS-CoV-2 treatment [76].

4.1.8. Favipiravir

It is another promising drug that is used to treat the infection of coronavirus and is a purine nucleic acid analog. According to various clinical trials, Favipiravir is an antiviral candidate and is found to be an RNA-dependent RNA polymerase inhibitor. In cells, the phosphorylated form of Favipiravir activates (Favipiravir-RTP) to inhibit the polymerase activity of viral RNA [77]. Mechanistically, Favipiravir is not fully known, but studies reveal that it acts as a substrate of the viral RNA polymerase that converts it into an active phosphoribosylated state. The drug is believed to obstruct the genomic RNA synthesis of the virus as a chain terminator [78]. It is found to be an RdRp inhibitor which has already been used as an intervention for the Ebola virus and is now used to prevent the SARS-CoV- 2 replication with an EC_{50} value to be 61.88 µM [62]**.**

4.1.9. Atazanavir/ritonavir

A deeper analysis of the coronavirus revealed that Main protease (M^{pro}) or the 3-Chymotrypsin like Protease is a proteolytic enzyme. It acts pivotally to cleave the replicase polyprotein 1ab in SARS-CoV-2. Orf1ab of the viral RNA genome is responsible for the translation of M^{pro}, it is also known as non-structural protein 5 (nsp5) and consists of 306 amino acids [79]. Furthermore, it has been recognized that there are 12 nsps (nsp4 and nsp6 to nsp16) involved in viral replication and its assembly. M^{pro} is also found to release these 12 nsps by cleaving the replicase polyprotein at 11 specific sites. Primarily, the enzyme is a dimer in structure with three domains on each monomer. M^{pro} is a promising drug target due to its functional significance in the SARS-CoV-2 life cycle and the presence of distinct recognition sites which are not possessed by human proteases [62]. In this regard, Fintelman-Rodrigues along with their co-workers recognized the potential of atazanavir alone and in combination with ritonavir for COVID-19 treatment [80]. Molecular dynamics and molecular docking revealed that atazanavir possesses the potential to target the active site of M^{pro}. Both drugs were also analyzed for their potential against SARS-CoV-2 in human epithelial pulmonary cell lines and Vero E6 cells. The drugs were found to inhibit SARS-CoV-2 in the above-mentioned two cell lines vigorously [62].

4.1.10. EK1C4

SARS-CoV-2 mediated cell-cell fusion is potentially inhibited by the derivatives of EK-1 that were designed by covalently linking palmitic (EK1P) and cholesterol (EK1C), when their IC_{50} values are 69.2 nM and 48.1 nM, respectively. Based on the success, further peptides were created (EK1C1 to EK1C7) with PEG-based spacers and glycine/serine-based linkers (GSG). Among them, EK1C4 is considered the most potent lipopeptide, having five optimal residue linker/spacer GSGSG-

PGE4. It is shown to possess potential activity against live SARS-CoV-2 infection and its pseudovirus infection when their IC_{50} value is 36.5 nM and 15.8 nM, respectively. Hence, EK1C4 can be considered a promising drug candidate against COVID-19 [62].

4.2. Indirect Therapeutic Drugs against the Virus

These drugs help the immune system fight against the virus but do not directly inhibit viral replication. They are more preferable than direct therapeutic drugs since they do not induce resistance to the virus.

4.2.1. Tocilizumab

Tocilizumab (TCZ) is a recombinant humanized monoclonal antibody, directed against soluble and membrane-bounded interleukin-6 (IL-6) receptors [81]. Monoclonal antibodies provide an efficient protective effect against these viruses as compared to vaccines [1]. TCZ was used for the treatment of many life-threatening cytokine release syndromes, such as severe rheumatoid arthritis and giant cell arteritis [82]. It is used to treat severe cases of COVID-19 since it helps to reduce the level of C reactive proteins [83]. Furthermore, when patients are at high risk of cytokine storm, treatment with TCZ showed clinical benefits [84]. It is officially approved for the treatment of COVID-19 in many countries including Italy, Pakistan, and China [85, 86]. TCZ is used to reduce the risk of invasive ventilation or death in a cohort of severe COVID-19 patients.

4.2.2. Chloroquine

It is an aminoquinoline and a broad-spectrum antiviral drug that is widely used as an autoimmune and anti-malarial drug [87]. It is used for the treatment of COVID-19 since it affects the glycosylation of ACE2 cell receptor, which is used by the virus to enter the host cell [88]. It also blocks the viral infection by increasing the endosomal pH required for viral cell fusion. It was highly effective against SARS-CoV and is potentially used for the treatment of COVID-19 [52, 89]. Some countries have officially approved the use of chloroquine against SARS-CoV-2 [90, 91].

Chloroquine was found to accumulate itself in Golgi-like organelles and those vesicles which are acidic, such as endosomes and lysosomes in their unprotonated state. These destinations ionize the chloroquine, which in turn increases their pH and inactivates various proteolytic enzymes. The virus requires acidic surroundings to enter, replicate, and cause infection in the endosome-lysosome. Hence, an increase in pH can efficiently prevent viral entry and replication [92]. It is also found to intervene in the interaction between ACE-2 receptors and viral spike proteins that are vital to allow the entry of the virus into the cell, indirectly. The affinity to SARS-CoV-1 S protein decreases when chloroquine hinders the Golgi-mediated glycosylation of ACE-2 at N-terminal. Therefore, a delicate interaction prevents viral entry into the cell [62].

4.2.3. Leronlimab

It is a humanized monoclonal antibody that binds CC-chemokine receptor-5 (CCR5). Evidence on Leronlimab suggests that it is an optimistic approach to treat coronavirus infection [93]; however, due to limited related investigations, it is not completely proven to deal with COVID-19 [78].

4.2.4. Camostat

Apart from ACE-2 receptors, SARS-CoV-2 is also assisted by transmembrane protease serine 2 (TMPRSS2), which is encoded by the TMPRSS2 gene. It is a host cellular protease, which is predominantly found in the cell membrane of epithelial lung cells. It also assists the priming of spike protein /to fuse the membranes of the cell and that of the virus. This is considered a crucial step for viral entry. Recently, it was identified that this entry can be prevented by camostat, an inhibitor of TMPRSS2 [94]. It is a serine protease inhibitor and was previously used to treat pancreatitis. It was recently found to inhibit the SARS-CoV-2 via TMPRSS2 inhibition. After the clinical trials, camostat might prove to be an efficient drug against COVID-19 [62]**.**

4.2.5. Nafamostat

It is another serine protease inhibitor and acts as an anticoagulant. It binds with the TMPRSS2-a transmembrane protease and prevents the SARS-CoV-2 entry into the cell when its EC_{50} value is 22.50 µM [89]. Nafamostat can also be considered a therapeutic drug against COVID-19 [62].

4.2.6. E-64-d

This is a cathepsin L inhibitor and assists camostat to inhibit the entry of SARS-CoV-2 [95]. Cathepsins are primarily cysteine proteases and are of immense importance during the catabolism of protein in lysosomes and endosomes. Cathepsin L is necessary for the entry of SARS-CoV into the host cell. Once inside the endosomes, cathepsin L activates the viral spike protein and releases viral genetic material into the cytoplasm after the fusion of endosomal membranes and the virus [62]. E-64-d is a covalent cathepsin inhibitor and is found to contain an epoxide ring that forms the covalent bond on its catalytic site when there is a nucleophilic attack by Cys-SH [96].

Table 1. Potential Therapeutic Drugs against SARS-CoV-2

Type of therapeutic drugs	Therapeutic drugs	Bioactivity	Clinical phase	References
Direct therapeutic drugs against the virus	Remdesivir	It is an adenosine analog that inhibits viral replication.	It is undergoing its 4th phase of the clinical trial against SARS-CoV-2 infection.	[5, 58, 59, 89]
	Lopinavir	It works as a protease inhibitor.	It is an approved as HIV medicine. It is undergoing clinical trial for the treatment of SARS-CoV-2 infection.	[52, 65]

Type of therapeutic drugs	Therapeutic drugs	Bioactivity	Clinical phase	References
	Emetine	It works as a protein synthesis inhibitor.	It is an approved treatment against severe amoebiasis in China. It is undergoing clinical trial for the treatment of SARS-CoV-2 infection.	[65]
	Homoharringtonine	It inhibits the replication of SARS-CoV-2.	It is approved by FDA and is used to treat chronic myeloid leukemia. It is undergoing clinical trial for the treatment of SARS-CoV-2 infection.	[65, 73]
	Ivermectin	It inhibits the host importin alpha/beta-1 nuclear transport proteins.	It is still not approved for the treatment of any viral disease.	[75]
	Favipiravir	It is a purine nucleic acid analog.	It is a promising drug candidate against SARS-CoV-2 infection.	[77]
	Aloxistatin	It is a cysteine protease inhibitor of cathepsins and calpains.	It is a promising drug candidate against SARS-CoV-2 infection.	[63]
	Viracept	It targets the SARC-CoV-2 spike S glycoprotein and inhibits the S-o and S-n-mediated cell fusion.	It is a promising drug candidate against SARS-CoV-2 infection.	[63]
	Atazanavir/Ritonavir	It targets the active site of $M^{pro.}$	It is a promising drug candidate against SARS-CoV-2 infection.	Faheem et al., 2020);[80]
	EK1C4	It possesses potential activity against live SARS-CoV-2 infection	It is a promising drug candidate against SARS-CoV-2	[62]

Type of therapeutic drugs	Therapeutic drugs	Bioactivity	Clinical phase	References
		and its pseudovirus infection.	infection.	
Indirect therapeutic drugs against the virus	Chloroquine	It interferes with the mechanism of Glycosylation in cellular receptors.	It is approved to be used against SARS-CoV-2 in some countries.	[52]
	Tocilizumab	It is a monoclonal antibody used to reduce the level of C-reactive protein in severe cases of COVID-19.	It is approved for the treatment of COVID-19 in some countries.	[85, 97]
	Leronlimab	It is a humanized monoclonal antibody, which binds with the CC-chemokine receptor-5 (CCR5)	It workings have not been investigated completely to prove its potential to manage the COVID-19.	[93 , 78]
	Camostat	It inhibit the SARS-CoV-2 via TMPRSS2 inhibition.	It is a promising drug candidate against SARS-CoV-2 infection.	[94, 62]
	E-64-d	It is a cathepsin L inhibitor.	It is a promising drug inhibitor against SARS-CoV-2 infection.	[95, 96]
	Nafamostat	It binds to the TMPRSS2.	It is a promising drug candidate against SARS-CoV-2 infection.	[62, 89]

4.3. Vaccines against the SARS-CoV-2

The COVID-19 pandemic has affected countries around the globe to cause social and economic disruptions. According to previous studies, antibodies play a crucial role against the spread of the coronavirus. Hence, antibodies act as protection against SARS-CoV-2. They are initiated into the body naturally or by vaccination to make it immune against the virus. Unfortunately, the mechanism of lasting immunity is still not recognized fully [98].

Vaccines appear to be the most efficient way to fight against new viral strains and reduce the prolonged incubations and outrageous prevalence of COVID-19. The

general strategy to design a vaccine involves the antigen, the adjuvant, the manufacturing system, and the functioning strategy to deliver it. The protein structure of the virus and its genome sequence was made accessible in a remarkably short duration. This was done to boost the development of attenuated or inactivated viral vaccines and other treatments as well as epitope mapping and bioinformatics predictions [99]. Many efforts are being made to develop an adequate vaccine. Most of the candidate vaccines are focused upon the S-protein of SARS-CoV-2 and based on protein sub-unit, live attenuated virus or inactivated one, nanoparticles, viral vector, RNA and DNA., each presenting its own challenges. Apart from this, researchers are also considering some adjuvants, such as CpG 1018 (Dynavax) and AS03 (GSK), to escalate the immunogenicity [100]. COVID-19 associated hospitalizations were notably reduced due to corona vaccines. It is anticipated that upcoming research on COVID-19 vaccine and drugs will significantly decrease corona-related issues and deaths.

It was observed that adult recipients of Moderna and Pfizer-BioNTech vaccines showed 94% effectiveness in the case of complete vaccination, while partial ones received 64% efficacy with 65+ years of age [101].

The United Kingdom was the first country to execute a vaccination program against COVID-19 on 8th December 2020. It approved the emergency use of Pfizer-BioNTech, which is an mRNA vaccine. Afterwards, Oxford-AstraZeneca was also added to the program. It is an adenovirus vector vaccine. Initially, vaccination was only given to frontline workers and individuals with age greater than 80. Later, it was also given to other age groups [102]. The vaccinated individuals complained about suffering from systematic symptoms such as chills, fever, fatigue, and headache, and local symptoms such as itching, bruising, redness and swelling. Many patients experience some of the above-mention dermal symptoms at the injection site, which commonly heals up within a few days. If symptoms do not get better, then SIRVA (shoulder injury-related to vaccine administration) may occur. It is a rare condition that occurs due to an improper injection technique [103]. Many options for vaccine development are under consideration to target the proteins and virions of the virus [31, 104] as shown in Table 2.

Table 2. Types of Vaccines against SARS-CoV-2

Type of vaccine	Bioactivity	Advantages	Disadvantages	References
DNA and RNA Vaccine	Targets the S Protein	Easy manipulation Immunogenic Rapid production	Safety issues Efficient delivery system required	[31, 104]

Type of vaccine	Bioactivity	Advantages	Disadvantages	References
Viral vector based vaccine	Targets the S Protein	Excellent clinical and preclinical results Successful against MERS-CoV	Negative effect of vector can disturb viral effectiveness	[31, 104]
Inactivated vaccine	Targets the whole virion	Easy process Successfully tested against SARS-CoV-1	Large amount of infectious virus need to be handled Causes hypersensitivity	[31, 104]
Live attenuated vaccine	Targets the whole virion	Excellent in induction of T and B cell response Simple process	Not suitable Risk of reversion to a viral strain Safety issues	[31, 104]
Recombinant protein vaccine	Targets the S Protein	No infectious virus required Adjuvants may be used	Limited production	[104]

5. Conclusion

This study performed a progressive literature review to summarize the innate and adaptive immune response and the availability of potential therapeutic agents as well as the vaccines against SARS-CoV-2. Type 1 Interferons (IFN), the innate immunomodulatory molecules, fight against SARS-CoV-2 by inhibiting viral replication at an early stage. However, adaptive immunity in patients and the production of antibodies, as well as antigen-specific B cells, reduces the viral infection. Furthermore, several direct and indirect therapeutic drugs have been used against SARS-CoV-2. Some of the available direct therapeutic drugs are Remdesivir, Lopinavir, Emetine, and Homoharringtonine, while the indirect therapeutic drugs used against SARS-CoV-2 are Chloroquine and Tocilizumab. The indirect drugs are used to enhance the immune response against the virus. Indirect therapeutic drugs are comparatively more efficient than direct therapeutic drugs since they do not cause drug resistance in the virus. There are various COVID-19 vaccine candidates under the consideration by many research institutes and pharmaceutical companies around the globe. Among them, the most effective vaccines are Moderna and Pfizer-BioNTech. They have an mRNA platform, having a significant success rate of up to 90%. Despite their efficiency, some inauspicious effects of the vaccination, such as headache, pain, and fatigue, were observed. Nevertheless, the

trial assay sensitivity supported mRNA vaccine. The occurance of mutation in spkie proteins would lead to streamlining the analysis of genome sequence to develop a sustainable vaccine.

Conflict of Interest

The authors declare no conflict of interest.

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