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Emergence of SARS-CoV-2: Insight in genomics to possible therapeutics

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Abstract

Rising of a new virus from city of Cathay, responsible for 2019 global pandemic is caused by SARS-CoV-2marked as a great threat for populations. The member (CoV-2) from vast family of Covid virus with single- stranded RNA spread to over 216 countries and billions of individuals died all around the globe. Regardless of all strict standard operating procedures, special care and therapies, SARS-CoV-2 mutating its genomic structure and leads to shutting the world. While different therapeutic approaches face problems due to the complexity in pathogenicity mechanism of CoV-2 and its variants. Mechanism of action, genome analysis, transmission, development of broad-spectrum antiviral medications and SARS-CoV-2 vaccines have been reported which are essential for future directions to control this pandemic. Here, in this review, these domains were discussed to highlight the genome structure pathophysiology, immune response, multiple diagnostic methods, and possible treatment strategies. This review deliberates the methodologies for creating practical vaccinations and treatment cocktail to manage this eruption.

Introduction

Beginning in the twenty-first century (2020) which was a challenging year as zoonotic coronavirus has infected human populations after overcoming the species barrier by causing respiratory infections, pneumonia, and intestinal diseases, etc. The situation became worst when a new infectious pathogen was emerged and recognized in Wuhan, affecting people exposed so as to fresh seafood market. Initial reports suggested that this virus is transmitted from person to person, but to what extent remains unknown [1]. This highly pathogenic virus-infected a huge number of people resulting in many deaths very quickly in China. This epidemic disease was given a provisional identity as 2019-nCoV. The 11th of February 2020, World Health Organization named this 2019-nCoV as COVID-19 (Coronavirus disease). The International Committee on Taxonomy of Viruses (ICTV) turned provisional identity 2019-nCoV into SARS-CoV-2 [2-4]. According to WHO reports, SARS-CoV-2 has infected people in over 216 countries including the regions of America, Europe, Southeast Asia, the Eastern Mediterranean and Africa. It has been described that by WHO there have been27,645,426COVID-19 confirmed cases and 898,111 Confirmed deaths worldwide until September 10, 2020, with a global death rate of 3,502,901 by May 20, 2021 [5]. In December 2019, there was huge transmission in a matter of weeks in Wuhan by means of person-to-person contact. The transference of this novel coronavirus spread this infection during the Chinese New Year holidays by national and international traveling [6].

In the epidemic of COVID-2019 in China, the early genetic analysis reported that this virus found the closest genetic similarity with the coronavirus isolated from a source of zoonotic disease. The pathogen was discovered to be similar to SARS-CoV but different. More evidence in recent months has clearly shown the significant differences between COVID-19 outbreaks and characteristics compared to SARS-CoV [7]. COVID-19 appears to spread in the same way that other common cold or influenza viruses do. Direct contact with infected people's sneezes or coughs spreads the virus but the function of fecal-oral transmission in COVID-19 has still to be decided [8].

The above-mentioned viruses were only meant to infect animals, but the rest of the world experienced the extreme acute respiratory syndrome (SARS) outbreak in 2002, which was caused by SARS-CoV and few years later in 2012,Middle East respiratory illness coronavirus caused an endemic in Middle Eastern nations [9,10]. The SARS and MERS epidemics revealed the possibility of transmission of this newly discovered SARS virus (CoV-2 virus) from animal to human and human to human [11]. The genetics of SARS-CoV and MERS-CoV are very much identical in sequence and encode crucial enzymes and proteins like a spike, envelope and nucleocapsid proteins [11]. Following that in the end of 2020, an unpredicted increase of pandemic cases indicated about the variants such as 501Y.V1 (B.1.1.7) in UK and 501Y.V2 (B.1.351) in South Africa [98]. In South Africa, highly disseminated transference in regard to highly populated region and immunity might have supported every development and ensuing spread of the variation. A mutation (N501Y) in the spike protein's receptor-binding domain was found in variants that is accounted for to add to expanded transferal up to 70% increased transferal [99].The spike protein of the 501Y.V2 variant includes two extra transformations (E484K and K417N)that gives likely resistance getaway to antibodies. Regarding evolution, in Manaus, Brazil, a new P.1 (501Y.V3) lineage with additional mutations (N501Y, E484K, and K417T) has been identified [100].

Presently, the universe is managing this worldwide pandemic and thus, there are prompt requirements to evolve systems that can be involved in the COVID-19 therapeutics. Therefore, it is imperative to conduct an extensive analysis of its genomic structure, viral entry, pathogenesis and transmission of SARS-CoV-2. The aim of the current review is to evolve these parameters and this study also analyzes the current COVID-19 diagnostic approaches and therapeutic methods.

Methods

Search Strategy and Selection Criteria

By entering relevant terms such as "Emergence of Covid-19", genomics of SARS-CoV-2, Virus entry, Replication, Transmission and Pathogenesis of SARS-CoV-2, a thorough search was conducted using Google Scholar and Google Web Browser. Different diagnostic techniques and therapeutic interventions were also found by Google Web Search. The literature that was found underwent additional screening for inclusion based on their substance. 100 peer-reviewed research publications were chosen for this investigation.

Discussion

Genome analysis of SARS-CoV-2

Coronaviruses are the members of the order Nidovirales' subfamily Coronavirinae, which consists of four genera. Four genera of this subfamily include *Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus*. The genetic material of coronaviruses employed RNA as a template to generate a single-stranded positive-sense RNA with a 3′ poly-A tail and a 5′ cap structure [12-15]. All coronaviruses typically contain crown-shaped peplomers with 80-160 nM in size and 27 to 32 kb positive polarity [16, 17]. The S protein in the SARS-

CoV-2 receptor-binding domain (RBD) region may have undergone genetic recombination and could explain why CoV-2 has a higher transmission rate than SARS-CoV [18]. A novel coronaviruses named as SARS-CoV-2 genomic structure shows 88 % similarity to the sequence of two bats (bat-SL-CoVZC45 and bat-SL-CoVZXC21) and approximately fifty percent genetic similarity to the MERS-CoV. Due to similarity with typical coronaviruses, SARS-CoV-2 comprises almost 10 ORFs which are flanked by 5′ and 3′ UTRs as shown in figure 1 [101]. The first open reading frames (ORF1a/b), which contains about two huge polyproteins are produced from two-thirds of the viral RNA.The two polyproteins pp1a and pp1ab in SARS-CoV and MERS-CoV translated into sixteen nonstructural proteins (nsp1-nsp16). The nonstructural proteins are used to form the viral replicas transcriptase complex [19].

Layers of rough endoplasmic reticulum rearrange those nonstructural proteins in the double-membrane vesicles. The viral transcription and replication occur in these membranes. The other open reading frames of CoV-2are one-third of the total genome encoding four structural proteins and many other proteins, which do not take part in the viral replication [20, 21]. According to an amino acid phylogenetic tree, the S1 protein of pangolin coronaviruses was firmly linked with SARS-CoV-2.CoV-2 and pangolin-CoV were found in the RBD region shares a highly conserved sequence with single amino acid change. This one amino acid change is not in the region of five residues, which are involved in the binding with human ACE2. Pangolin coronavirus genome shared a 91.02% nucleotide identity in conjugation of genome of novel coronavirus SARS-CoV-2 [22-24].

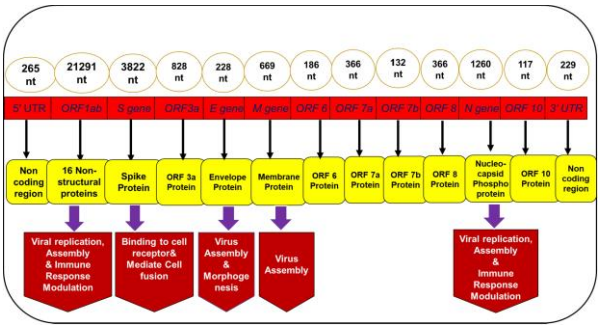

Figure 1: Genomic organization of SARS-CoV-2 showing arrangement of open reading frame [101].

Viral entry & Replication

The spike proteins aid in receptor binding and membrane fusion, as well as assessing the host's capacity for tropism and transmission. Coronavirus spike proteins are typically classified into two domains.The domain S1facilitates the receptor binding, and the domain S2, responsible for cell membrane fusion [25, 26]. CoV-2 has a similar cell entry receptor ACE2 (Angiotensin-converting enzyme 2) as SARS-CoV.SARS-CoV transmission can occur between species as well as between humans are regulated by ACE2. This protein ACE2 dispatched in alveolar cells, intestinal epithelium, and vascular endothelium. As a result, the SARS-CoV-2 protein binds to the ACE2 protein found in the lower respiratory tract of humans, results in acute lung injury and pulmonary edema. The receptor ACE2 on the surface of human cells is where the coronavirus's S proteins on its surface bind as shown in figure 2 [27, 28].

Along with the receptor-binding domain, the S1 domain is in charge of cellular tropism and virus-host range [29, 30]. As a result of membrane fusion, the viral genomic RNA is transferred into the cytoplasm and then translates into two polyproteins pp1a and pp1ab. These polyproteins construct a replication-transcription complex in double-membrane vesicles and serve as a conceal for nonstructural proteins [31, 32]. Complex replication-transcription replicatesitself indefinitely uninterruptedly and forms nested set of sub-genomic RNAs encoding the structural proteins and several other accessory proteins [33,34]. Another study found that the binding efficacy of SARS-CoV-2 S protein ACE2 is ten to twenty times higher than SARS-CoV [35]. It was reported that the lungs seem to be the most susceptible target organ to the virus. The wide surface area of the lungs might be the reason that makes them a vulnerable target to inhaled viruses. There is another reason that alveolar epithelial type II cells (AECII) made up 83% of the ACE2-expressing cells [36].

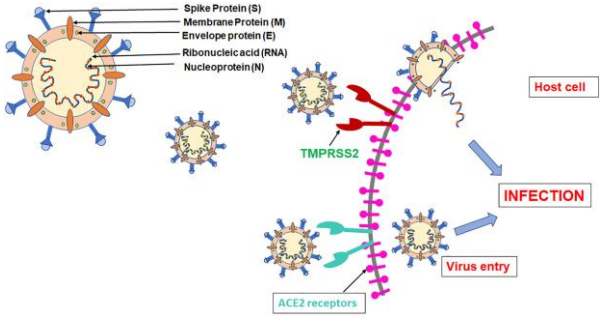

Figure 2: Graphical representationpresents a high-level overview of how ACE2 and TMPRSS2 involved in the life cycle of SARS-CoV-2. The PPs so produced are then processed into 16 unique NSPs by two major proteolytic enzymes, SARS-CoV-2 Mpro and PLpro [101].

Pathogenesis and immune responses

The innate immune response identifies pathogen-associated molecular patterns (PAMPs) produced by a virus invasion to enable an antiviral response. PAMPs are present in RNA viruses, such as coronavirus, either as single-stranded or double-stranded viral genomic

RNA.The endosomal RNA receptors TLR8 and TLR7 in ssRNA, as well as the cytosolic RNA sensor RIG/MDA5 (retinoidinducible gene), are used to identify these molecular structures (PAMPs) [37-39]. This conceding activates various signaling pathways and transcription factors, including activator protein 1 (AP1), nuclear factor B (NFB), and interferon response factor 3 along with their nuclear translocation.This identification triggers the activation of many signaling pathways and, as a result, the nuclear translocation of nuclear factor-kB (NF-κB), activator protein 1 (AP1), interferon response factor 3 (IRF3), and IRF7 transcription factors. NFkB (Nuclear factor-kappa B) and AP1 trigger expression of genes that are necessary for the encoding of molecules [40, 41].

The main cytokines in host's defense in case of viral infections are type I interferons. They do, however, encourage the activation of genes that produce antiviral proteins. These proteins serve an important function as mediators in viral replication inhibition and modulating the actions of suppressor T cells [42]. It reported ARDS are the leading cause of death, as well as the primary event in MERS-CoV and SARS-CoV infections The cytokine storm is systemic uncontrollable inflammatory response is an essential mechanism for ARDS [43, 44]. This lethal and uncontrollable inflammatory reaction is caused by the production of enormous quantities of pro-inflammatory cytokines(IFN-α, IFN-γ, IL-1β, TNF-α, etc.) and chemokines such as CCL2 by immune effector cells in morbidity with SARS-CoV [46-48]. In case of severe infection, this cytokine storm can trigger an aggressive immune system attack on the body resulting in multiple organ failure and ARDS, both of which can lead to death [44].

The acquired immune response to viral infection consists primarily of antibody development against viral antigens, as well as humoral immunity. Cellular immune response is the utmost essential aspect in viral elimination. T CD4+, on the other hand, detects the antigens that MHC-II presents on the surface of APCs. The CD4+ cells then perform numerous critical activities, including the constant stimulation of B cells and macrophages that are specific for the antigen.TNF- and IFN cytokines are produced by CD8+ cells, which also destroy virus-infected cells, which help to suppress viral replication. Viruses can evolve immune evasion strategies to live longer, and then proliferate until they cause significant harm to the host [48]. After the viral entry into the cells,its antigen will be delivered to the antigen presentation cells, which are the key component of the body's anti-viral immunity [49]. The body's cellular and humoral immunity are then stimulated by antigen expression, which is aided by virus-specific B and T cells. The antibody profile against coronaviruses shows a classic pattern of IgM and IgG provision in all common acute viral infections. However, the IgG antibody can survive for a long time, indicating its importance in defense [50].

Transmission

It was suggested that people might use the infected live animals or birds from the seafood market. Further research revealed that some people were infected with this virus despite never having visited a seafood market. These findings demonstrated that The virus can be transmitted from person to person as a result of intimate exposure to infectious individuals exposed to aerosols from coughing and sneezing [51-54]. There are many factors, which are concerned in transmitting the SARS-CoV-2; these conditions included environmental factors and human behavior. In some latest studies, it has been reported the presence of coronavirus in the sewer although no evidence confirmedSARS-CoV-2 transmission through sewage or contaminated potable water [55].

While environmental elements and circumstances that is humidity, wind and temperature speed have been employed in a few studies to determine their involvement in the survival and dissemination of COVID-19. However, the incidence of COVID-19 has reduced in numerous cases as humidity, wind speed, and temperature have increased. Although the virus is stable in pH ranges ranging from 3 to 10, at room temperature[56]. According to WHO sunshine, high or low pH, and heat make it easy to kill the coronaviruses [57]. The link between temperature and mortality rate is also influenced by environmental variables. According to one study, a rise in daily temperature impacts the frequency of instances of SARS-CoV-2 infection. A negative relationship was found among a country's temperature and the frequency of positive SARS-CoV-2 cases [58].

Diagnostic & detection methods

With a patient's contact history and clinical signs of infections, laboratory detections and radiographic imaging are not always convenient.Therefore, COVID-19 diagnostics have been facing much more difficulties [59]. Genome sequencing, Enzyme-linked immunoassay and ELISA and RT-PCR like laboratory detection methods have been used for diagnosis. As the clinical features of coronavirus are diverse and changing day by day, so detection of disease severity and evaluation is highly dependent on history and experience [60]. At the beginning of the COVID-19 disease outbreak, genomic sequencing used to detect the disease-causing infectious agents. This strategy was very expensive and complex in order to identifySARS-CoV-2 on a large scale.

PCR based Methods

Real time-PCR procedurebased on the N gene and the spike gene established by the Chinese CDC and many other companies was used on large scale in order to identify viral RNA [61-64]. The method of RT-PCR was considered as a gold standard, although had few restrictions such as nasopharyngeal swab's short detection window,false sampling and inconsistency of sample preparations [65, 66]. The RT-PCR method could make unreliable results. The Chinese CDC distributed urgently, NP and ORF1ab areas on the CoV-2 genome are intended to be detected by a fluorescence-based quantitative PCR tool.The two sets of primers were not always in agreement, which might lead to conflicting findings. Furthermore, deletions and mutations that happened throughout viral evolution in the SARS-CoV-2 genome may result in erroneous RT-PCR findings. The type of material utilised and the time it was collected for RT-PCR are also critical criteria in SARS-CoV-2 diagnosis [65].

Antibody-based Methods

ELISA (Enzyme-linked immunoassay) was strongly advised to increase COVID-19 detection rate since collecting blood was easier than nose or oral swabs for viral detection because antibodies had a considerably larger detection window than viruses [61]. Caution related to the ELISA method is that N protein is the most conventional viral protein in the human β-coronavirus, which may generate false-positive results. The used antigen might react with antibodies to other prevalent human coronaviruses. Common human coronaviruses that may generate during common colds [67]. The S protein could be the best candidate for the development of ELISA [61]. At that time, the most common methods of diagnosis used are RT-PCR (reverse transcription] or real-time PCR. These methods are made by using the RNA sample from the oropharyngeal swabs, sputum, nasopharyngeal aspirate. The lower respiratory tract has a higher viral load and genome section than the upper respiratory tract [68].

CRISPR-based approach

CRISPR is a well-known biotechnological method for amending the genome.Repeats (CRISPR)are nucleic acid sequences and a group of bacterial enzymes can identify and cut it such asCas9, Cas12, and Cas13 [69]. Using CRISPR technology, many research organizations across the world have discovered a viable approach for SARS-CoV-2 detection.The CRISPR-based technique used Cas13 to target two viral genes known as the ORF1ab gene and the S gene.In this protocol, synthetic viral RNA fragments were used as input. The CRISPR based SHERLOCK technique is a highly sensitive technique. The CRISPR based methods of detection do not require complex instrumentation and can give results in timeless than an hour. Besides this identification CRISPR Cas13, the method can also be utilized to treat COVID-19 patients [69, 70].

Microarray-based detection

SARS-CoV-2 can also be diagnosed using gene microarray technique. Microarrays would be a superior tool for detecting viruses with a high mutation rate. Guo et al [71] developed an SNP DNA microarray approach for detecting and genotyping SARS-CoV.In this study, 19 SARS-CoV patients provided a target of 24 SNPs, and the PCR amplified product was hybridised with the microarray. Microarray-based diagnostics and detections may be a superior choice for SARS-CoV-2 detection. As PCR-based approaches can only detect a limited number of genes in a single assay but microarray-based methods can identify a greater number of genes [71, 72].

Potential therapeutic options and preventive measures

Potential therapeutic options

The novel SARS-CoV-2 virus does not currently have an effective antiviral treatment., however numerous medications have been utilised to suppress the infection. Remdesivir and chloroquine have been shown in vitro to be particularlyefficient at preventing COVID-19 infection. Treatment with remdesivir alone or in combination with interferon beta or chloroquine proved extremely successful in controlling SARS-CoV-2 infection [73]. Broad-spectrum antiviral like dsRNA - activated caspase oligomerizer (DRACO) could be used to evaluate its efficacy against the treatment of SARS-CoV-2, as they were effective against a broad spectrum of viruses. This antiviral specifically causes host cells that are infected by the virus to undergo apoptosis but alone it is unable to prevent a virus from entering or damage the viral nucleic acids[74]. Remdesivir may compete for RNA-dependent RNA polymerase (RdRp) against RNA viruses [75]. The first COVID-19 patient in the United States was treated with Remdesivir and the patient's clinical condition improved after only one day of treatment [76].

Remdesivir is being studied in a phase 2 placebo-controlled study as a possible therapy for adult patients diagnosed with SARS-CoV-2 in hospitals by U.S. National Institute of Allergy and Infectious Diseases. A Phase III clinical study's findings have been released by Gilead Sciences about the useof remdesivir in hospitalised patients with mild Covid-19 pneumonia. The studies comparing clinical benefits after five-day and ten-day regimens of the medication to usual treatment [78]. However, a number of other antivirals are now being established for infection such

asNafamostat, Ribavirin, Favipiravir, Ritonavir, AAK1 and Arbidolshowedrestrained results against infection in in-vitro trials [69, 72, 79, 80]. Existing drugs, which can be used to combat this novel coronavirus and have some potential to control the infection.Therapeutic agents targeting this novel corona virus must have a potential to target the coronavirus replication and transcription-related enzymes and proteins, viral nucleic acids, nucleosides, and nucleotides asshown in (Table 1). The antiviral activity of Lianhuaqingwen has been used against the novel virus SARS-CoV-2 shows anti-inflammatory activity to regulate the host immune response. This strategy would exhibit the pharmacological potential to control the outbreak of SARS-CoV-2 by inhibiting virus replication [90].Many clinical studies found a higher concentration of cytokines in severe patients of SARS-CoV-2. This may be suggested that disease severity is associated with the cytokine storm [91]. Hydroxychloroquine (HCQ) is a derivative of chloroquine, which was used in vitro trials for their antiviral activity. HCQ is a less toxic and potent anti-inflammatory drug that may contribute to attenuate the inflammatory response in SARS-CoV-2 patients by inhibiting the viral entry and post-entry steps in a cell. Further studies and clinical trials needed to achieve efficient and safe results for HCQ to combat the COVID-19 disease [82].

Convalescent SARS-CoV patients exhibited a neutralizing antibody response, which can be identified even 24 months after infection. SARS-CoV recombinant S protein and deactivated virus persuade neutralizing antibody responses [92]. This approach could suggest some defense against SARS-CoV-2 that may have implications to control this outbreak. In the treatment of severe patients, the Convalescent Plasma therapy would be a feasible therapeutic choice with little risk.The high concentration of neutralizing antibodies in one dose of convalescent plasma be able to reduce the viral load. This method would be likely to be most effective in patients before they develop a humoral response to SARS-CoV-2. However, there is a need to investigate CP therapy in random clinical trials on a pilot scale to improve clinical outcomes. This method would be likely to be most effective in patients before they develop a humoral response to COVID-19 [93]. SARS-CoV-2 used the angiotensin-converting enzyme 2 (ACE2) as the cell entry receptor.Furthermore, fusion proteins neutralise virus pseudo-typed with SARS-CoV-2 spike proteins in vitro and might be used to diagnose and treat COVID-19 [94].

Drug repurposing is the process of finding new targets for medicines that are already on the market. It is assumed to be a practical and economical approach. According to estimates, 75% of currently accessible medications might be employed for the treatment of a range of diseases [113].

Repurposing existing medications to treat multiple diseases has recently gained popularity because it uses safe compounds with well-known pharmacodynamics, pharmacokinetics and preclinical profiles can skip the late clinical trial stages, making the drug development procedure more efficient, less expensive, and quicker [114].

1. Potential therapeutics that target SARS-CoV-2-related (genomic) targets

Remdesivir and Favipiravir

Remdesivir potential mode of action for treating COVID-19 involves inhibiting viral replication. SARS-CoV-2 replication requires the RNA-dependent RNA polymerases (RdRps) enzyme [113]. Remdesivir-TP faces competition from adenosine-triphosphate in order to be inserted into viral RNA chains in the embryo. RDV-TP terminates RNA synthesis before integrating into viral RNA because it does not cause instantaneous chain termination [115].

Individuals with severe COVID-19's clinical symptoms were improved by Remdesivir, according to a clinical research conducted in the US [116]. The only repurposed medication currently approved by the USFDA for severe COVID-19 symptoms is Remdesivir [117].

Favipiravir, a purine nucleotide prodrug that becomes active asfavipiravir-RTP(favipiravir-ribofuranosyl triphosphate) in tissue, operates by blocking the RdRp enzyme of the SARS-CoV-2. It makes it simple to incorporate favipiravir into viral RNA and sparing the human DNA and producing virucidal action. In China, a clinical research found that giving favipiravir to COVID-19 patients resulted in faster viral load clearance and improved lung CT scans than alternative treatment options. Russia, Turkey andJapanare among the nations where favipiravir is used as an approved antiviral drug [118].

Ivermectin and Molnupiravir

A macrocyclic lactone with numerous antihelminthic properties is ivermectin [119]. Additionally, it protects S protein, which binds to ACE-2 and the transmembrane receptor CD147. Ivermectin has been shown to have anti-inflammatory characteristics in mouse research, which may aid in the reduction of the cytokine storm in CoV-2 [120]. According to Mahmud et al., ivermectin and doxycycline work well together to treat mild to moderate COVID-19 [121].

The ribonucleoside analogue prodrug of -D-N4-hydroxycytidine is known as molnupiravir. It has been demonstrated thatwith low cytotoxicity and high resistance, it can stop the replication of several viruses.

When a drug's active form is integrated into a virus as a substitute of cytosine or uracil during the synthesis of RNA, this results in dose-dependent C to Uand G to A conversion that cause lethal mutagenesis throughout the whole genome of many viruses [122].

AT-527 and Niclosamide

By specifically inhibiting RdRp, AT-527 is a guanosine nucleotide analogue double prodrug, has demonstrated efficient both in vivo and in vitro efficacy against the HCV(hepatitis C virus). In an in vitro investigation, where AT-527 has significant action for COVID-19 [123]. An approved medication for treating tapeworm infection is niclosamide. It functions by enhancing autophagy, which reduces coronavirus replication, and suppressing S-phase kinase-associated protein-2 activity. This method might also be used to attack SARS-CoV-2. Niclosamide has been demonstrated to inhibit SARS-CoV-2 at the sub-molecular level [124]. In severe COVID-19 patients, niclosamide has been proven to reduce cytokine storms in clinical trials [125].

Nitric oxide (NO) andPF-07321332(Nirmatrelvir)

The clinical trial for Pfizer's second-generation medication PF-07321332, which targets 3CLpro to prevent viral replication, is now underway. Because it controls viral replication, 3-chymotrypsin-like protease (3CLpro) is a notable target and intriguing possibility for rational-based antiviral research [126]. The FDA has not yet approved protease indicators for SARS-CoV-2, despite the fact that they are routinely indicated for other viruses [127].

Three enzymes in mammalian cells, including inducible nitric oxide synthase(iNOS), endothelial (eNOS), and neuronal (n NOS), produce the essential agent nitric oxide (NO). NO is an essential component of the lungs and is required for controlling vasomotor tone in the lungs (Chavda et al., 2021e) [128] iNOS activity is often elevated during SARS-CoV-1 infection, and through cytotoxic processes involving the intermediate peroxynitrite, NO inhibits viral replication [129]. SARS-CoV-2, on the other hand, attacks endothelial cells, a significant source of NO production. As a result, restoring endothelial function and lowering inflammatory response may ensure the success of the use of inhaled NO in the treatment of SARS-CoV-2 infections [130].

Vaccines

Effective vaccines are needed to combat pandemicsinstigated by SARS-CoV-2 viral attack which is spreading with each passing day and the number of fatalities increases day by day. Vaccines are required at anurgent basis while previous vaccines like Covid-19 patients were the test subjects for live attenuated SARS vaccines and it may be effective.

Sr. No	Existing Antiviral Drug	Mechanism of action	Reference
1	Arbidol	an inhibitor that may interfere with viral envelope protein attachment to host cells and so hinder viral entrance into the target cell	[81]
2	Baricitinib	a JAK (Janus kinase] inhibitor might obstruct with the inflammatory practices	[80]
3	Chloroquine and Hydroxychloroquin	a drug that can raise endosomal pH and affect with ACE2 glycosylation	[73][82]
4	Favipiravir (favilavir]	Nucleoside that may act as an alternative substrate for the incorrect synthesis of viral RNA	[83]
5	Lianhuaqingwen (LH]	Inhibits viral replication and shows anti-inflammatory activity to regulate the host immune response	[84] [85]
6	Lopinavir	Protease inhibitors which may constrain the viral proteases	[79]
7	Nitazoxanide	This may obstruct viral protein expression	[86]
8	Remdesivir	Nucleotide analog may stop viral replication by inhibiting the viral nucleotide synthesis.	[87]
9	Ribavirin	A drug that interrupts RNA metabolism mandatory for viral replication.	[88]
10	Ritonavir	Protease inhibitors which may constrain the viral proteases	[89]
11	K22	Inhibit RNA synthesis by targeting virus membrane-bound replication complexes	[102]
12	DRACO	Induces apoptosis of cell containing virus by targeting dsRNA of virus	[103]
13	Bcx4430	Inhibits viral RNA synthesis and mRNA capping by targeting RNA dependent RNA polymerase	[104]
14	Aryl diketoacids (Adks)	Prevents helicase from its unwinding	[105]
15	JI103	Cause changings in phospholipids and target lipid membrane	[106]
16	Recombinant interferons	Induce the response of innate interferons against the virus	[106]

Table 1: Existing Antiviral Drugs with pharmacological Potentials against COVID-19

Based on the recent COVID-19 outbreaksvaccines based on viral vectors, viral-like particles, and recombinant protein have been designed against SARS -CoV-2 infections [95]. However, mRN-based vaccines have been used in a trial of phase one by US National Institute of Allergy and Infectious Diseases and soon will be available for human trials [18]. Different newly developed vaccines that have potential for SARS-CoV-2 going through their trial phases 1 and 2 are mainly antiviral, antibody, cell-based or RNA-based to be proposed [107]. Ad5-nCoV is the first reported vaccine from China with the Adeno virus type 5 replication defective to express spike proteins of SARS-CoV-2 and the study is due to be completed in December 2021 [108]. ChAdOx1 nCoV-19 vaccine made by using the technique of adding viral genetic material of SARS-CoV-2 into the ChAdOx1 construct that is used to make

spike glycol-proteins [109]. Other vaccines such as INO-4800 vaccine, mRNA-1273 vaccine, Covid-19/a APC vaccine, LV-SMENP-DC vaccine, bacTRL-Spike vaccine will soon complete their trials at the end of 2021 [110]. But the urgency is required along with safe procedures to develop promising vaccine candidate which fulfill all necessary characteristics of good vaccination.

The onset of the pandemic triggered a race to produce a vaccine in an effort to build herd immunity and decrease the negative consequences of COVID-19.The work being done to create a vaccine is currently showing results [111]. The WHO approved the Pfizer COVID-19 vaccine (BNT162b2) for emergency use on December 31, 2020. The AstraZeneca/Oxford COVID-19 vaccine was produced by the Serum Institute of India and SKBio on February 15, 2021, and the Ad26.COV2.S, developed by Janssen (Johnson & Johnson) on 12 March 2021 and Moderna was produced most recently on April 30, 2021 [112].

As of August 2022, 40 vaccinations are approved in at least one country worldwide. Additionally, the World Health Organization has granted the Emergency Use Listing (EUL) to eleven vaccines.The list of RNA and protein based vaccines and their efficacy after controlled trials conducted by different studies. (Table 2).

Vaccine	Manufacturer	Countries in Use	Efficacy in infection	Efficacy in severe disease condition	Ref.
Comirnaty (BNT162b2)	Pfzer/BioNTech	146	91.3%	96.7%	131
Spikevac (mRNA-1273)	Moderna	87	93.2%	98.2%	132
Vaxzevria (ChAdOx1 nCoV-19, AZD1222)	Oxford/AstraZeneca	141	74.0%	100%	133
Ad26.COV2.S	Janssen (Johnson & Johnson)	111	52.4%	74.6%	134
Covaxin (BBV152)	Bharat Biotech	14	77.8%	93.4%	135
Covilo (BBIBP-CorV)	Beijing Institute of Biological Products/ Sinopharm	91	78.1% 100%	100%	136
CoronaVac (PiCoVacc)	Sinovac Biotech	56	83.5% (Turkey)	100% (Brazil)	137
onvidecia (AD5-nCoV)	CanSino Biologics	10	57.5%	91.7%	138
Novavax	Nuvaxovid (NVX-CoV237	38	90.4% (US&Mexico)	100%	139

Table 2: Approved RNA and Protein based vaccines and their efficacy
*Performance under ideal and controlled trials is referred to as efficacy.

Preventions

The WHO declared a public health emergency of global concern on January 30, 2020. The SARS-CoV-2 outbreak is becoming a worldwide danger. There is currently no particular vaccination or therapy for COVID-19; thus, the best way to deal with this virus is to stop its transmission. Individuals infected with the virus should be detected early and treated using advanced technology and appropriate isolation. People who have close contact with sick persons should be confined and monitored on a regular basis. Healthy people should be aware that they can protect themselves by wearing a protective mask, staying at home, keeping social distance, and avoiding public gatherings. These precautionary measures will aid in the containment of the COVID-19 pandemic [96].

The COVID-19 epidemic has altered our way of life and will continue to do so in the future.In the not-too-distant future, remote learning and employment are likely to become viable alternativesas people are generally more willing to wear masks and get vaccineshots in daily life.

Conclusion

The COVID-19 pandemic has developed into a frightening menace to healthcare workers and the population of the world.Due to the limited knowledge regarding this emerging virus and antiviral drugs and vaccines for this disease are under development. The only option we have at that time is to control the infection by taking preventive measures. The implementation of these measures could prevent the spread of SARS-CoV-2 by monitoring the human-to-human spread of this virus. Government and Authorities in public health should continue to monitor the situation by inhibiting the social movements and suggest measures to reduce the transmission.It's necessary to introduce some brand-new, robust, and risk-free methods for SARS-CoV-2 detection.This pandemic is a public health emergency all over the world therefore, all countries needed to do organized international efforts to combat this disease.

Competing Interest

The authors declare that there is no conflict of interest.

Author Contributions

Conceptualization and original draft preparation, SS and SA; draft writing and data analysis, SS and AT; Manuscript revisions and final draft preparation SS and AT; Supervised the manuscript, AI and SA.The published version of the manuscript has been approved by all authors who have read it.

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