**Promiscuous Biological Features of Newly Emerged SARS-CoV-2 Facilitate its Unrestrained Outbreak: An Update**

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1. **INTRODUCTION**

More than 77 million cases of the coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been detected worldwide as of 22nd December 2020. The COVID-19 pandemic disease manifests a distinctive set of overlapping symptoms with that of other coronaviruses mediated infections.

Coronaviruses belong to the family of *Coronaviridae*, subfamily *Orthocoronaviridae*, comprising four genera i.e. Alphacoronaviruses, Betacoronaviruses, Gammacoronaviruses, and Deltacoronaviruses. The members of alpha and beta coronaviruses generally infect mammals and humans, while gamma and delta members infect birds. Human coronaviruses cause upper respiratory tract infections (mild to moderate) including 229E (Alphacoronavirus), NL63 (Alphacoronavirus), OC43 (Betacoronavirus), and HKU1 (Deltacoronavirus).

SARS-CoV-2, SARS, and the Middle East Respiratory Syndrome (MERS) belong to the genera of betacoronaviruses. SARS (China) and MERS (Saudi Arabia) are the two coronaviruses that caused a fatality in the years 2002 and 2012, respectively. The mortality rate of SARS was around 11%, while in the case of MERS, the mortality rate shot up to relatively greater extent (37%). This review aims to discuss the promiscuous biological features of novel SARS-CoV-2 as well as the current updates in terms of vaccine strategies under investigation globally.
Historically, the first human coronavirus was discovered by Tyrrell and coworker in the 1960s [1]. The genome of Coronaviridae is generally comprised of a single-stranded, enveloped, positive-sense RNA which ranges from 26 to 32 kilobases (kb) in length, encompassing a 5′-terminal noncoding region. This region is known as an open reading frame (ORF) 1a/b coding region, an s region encoding the spike glycoprotein (S protein) [2, 3]. Other regions of the genome are ‘e’ region encoding envelope protein E, ‘m’ region for M protein, ‘n’ region that encodes nucleocapsid N protein along with noncoding 3′-terminal region (Fig. 1).

The main three characteristics (replication, transcription, and translation) of the virus genome are typically guided by the region of ORF 1a/b, which can be cut by 3C-like proteases (pro and papain-like) of the viruses to form RNA-dependent RNA polymerase and helicase enzymes [4].

Coronaviruses are spherical and possess protruding spikes on their surface, giving the particle a crown-like appearance. The spike interacts with human cells and permits the virus to enter within the host cells. Under the electron microscope, coronavirus (SARS-CoV-2) is somewhat like a Pincushion fruit (Neolamarckia cadamba Roxb.) in appearance with a diameter of roughly 60-140 nm [5]. In general, a classic coronavirus (CoV) comprises about six ORFs in its genome, which produces several polypeptides. The two polypeptides, pp1a and pp1ab, are managed by virally encoded chymotrypsin-like protease (3C-like protease) or main protease (M-pro) and one or two papain-like proteases that lead to the formation of 16 nsps (nonstructural proteins). Amin et al. highlighted these two targets (Mpro and PLpro) from a structural and medicinal point of view, together with recently reported protease inhibitors’ in their report [6]. All the structural and additional proteins of SARS-CoV-2 have been reported to be translated from the subgenomic RNAs of CoVs. Principally there are four main structural proteins such as spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. Different CoVs may encode some individualized structural and accessory proteins, such as HE protein, 3a/b protein, and 4a/b proteins. These accessory proteins are crucial and perform several important functions that are fundamental for virus survival.

Fig. (1). The genome of typical coronavirus. Single-stranded, non-segmented, which is around 26-32 kb containing 5′- methylated caps and 3′-polyadenylated tails and is arranged in the order of 5′, replicase genes, genes for structural proteins (S), an envelope protein (E), membrane protein (M), nucleocapsid protein (N), polyadenylated tail and then finally 3′ end [4]. (A higher resolution / colour version of this figure is available in the electronic copy of the article).
Among various structural membrane proteins, the most common one is the membrane (M) glycoprotein, which spans the membrane bilayer 3-folds. The short NH\(_2\)-terminal domain lies beyond the exterior membrane surface. The virus has a long COOH terminus (cytoplasmic domain) interior core of the virion. The M and E proteins contribute to the composition of virus coat protein; on the other hand, the N protein is required for the makeup of the virus within the host. The S is typically a type I membrane glycoprotein which organizes the peplomers. It is considered to be the main inducer of neutralizing antibodies in the host. It exists between the envelope proteins and actively participates in the molecular interaction, and regulates the formation of the coronaviral membrane. The S protein is contemplated as the main protein to attack the host cells. The receptor of host cells comes in contact with the structural protein S of the virus. The M protein contributes a principal function in the intracellular formation of new virus bodies independent of S protein. The culture of CoV in the presence of tunicamycin leads to the creation of spikeless, non-infectious virions that contain M but devoid of S protein. The sign and symptoms of COVID-19 are mild fever, difficulty in breathing, dry cough, and invasive lesions on both lungs of the patients that may spread to the lower respiratory tract and finally cause viral pneumonia [7]. If not handled properly at the early stage, patients may suffer from dyspnea and respiratory distress syndrome. In most cases, the patient needs artificial life support for breathing. Male patients constitute more than two-thirds of the reported cases, and the mortality rate is more (1.5 times) in males as compared to females [8]. The viral load in the infected COVID-19 patients (sputum) reaches an optimum level after a few days of infection, while symptoms may last few weeks.

According to the surveillance report by the Center for Systems Science and Engineering at Johns Hopkins University, USA [9], the number of confirmed patients are more than 77,426,697, and the number of fatalities is 1,703,899 (as of 22nd December 2020) worldwide since the outbreak started in Wuhan Hubei, China in December 2019. The number of COVID-19 infected patients is rising exponentially in most of the countries day by day. The fatality rate is in the range of 3-4% (by March 2020) as compared with SARS and MERS. The recovered COVID-19 patients are around 45 million worldwide, but in China, the recovery rate is higher as compared with other countries. The COVID-19 has spread to several parts of the world and is considered to be more severe than SARS and MERS. There exist 10 clades of coronavirus; however, in India, the dominant one is A2a, which accounts for more than 50% of the cases. Recently, a new clade, A3i, which is different from the other 10 clades, has been reported predominantly in the South East Asian regions like India, Singapore, Vietnam, Brunei, Philippines, etc. The clade A3i is a unique strain of coronavirus as it has been defined by four mutations [10]. This clade has not been found in Europe or China. It is more prevalent in the south of India in the middle of February from South-East Asia. The data from a recent study advocates that in India, more than 41% of cases represent A3i, but the principal clade is A2a.

SARS-CoV interacts with angiotensin-converting enzyme 2 (ACE2) receptor while MERS binds to CD26 receptor [11]. The organisms that host coronaviruses range from avian family to mammals and wild animals (avian hosts, camels, bats, masked palm civets, mice, dogs, pangolins, and cats) [12]. The newly emerged coronavirus (SARS-CoV-2) diverges from SARS coronaviruses in the genomic sequence and is much more closely interrelated to the bat-derived HKU4 and HKU5 coronaviruses [13, 14]. The sequence identity of different patients of COVID-19 infected with SARS-CoV-2 obtained from Wuhan was found to be almost identical (99.9%). Epidemiological data of initial patients suggest that infection due to SARS-CoV-2 was originated from one source and, within a short period, spread very quickly. The normal evolutionary rate for coronaviruses is typically 10\(^{-4}\) nucleotide substitution per site per year, with mutations surfacing in each replication cycle [3]. The genetic mutability by recombination mechanism can be well correlated with error-prone replication, which is an essential mechanism of genetic variation and virulence. Exploiting this mechanism, SARS-CoV-2 became mutated and increased its virulence [15], while MERS has not able to change significantly since its inception in 2012. It has been reported that the mutation rate of strain A3i is slower than the other strains, namely A2a; the coronavirus, which originated in Wuhan, is B virus. This may be due to the slow rate of A3i spreading, even though A2a reached here at a later stage; however, it spreads faster [10].

2. ORIGIN OF COVID-19

Available data from various hospitals of the USA, China, and many European countries had confirmed that coronaviruses are more transmissible between humans than other animals. However, a few news reports from American zoos indicated that the members of the family Felidae too are susceptible to COVID-19 infection [16]. There is a lot of controversy regarding the origin and propagation of the COVID-19 strain. Even its genome has been considered to be engineered that ensued like a ‘Frankenstein.’ However, a parallel occurrence of SARS-CoV-2 had also been promulgated where a Japanese couple visiting the US was found to carry the virus back to their country. There is another speculation that viral infection existed in Italy in the same period. More importantly, the concerned SARS-CoV-2 strain prevailing in Italy was found to be more deadly and killed many of the infected patients. It is now confirmed by Andersen KG et al. that SAR-CoV-2 is neither genetically engineered in the lab nor a purposefully manipulated virus [17]. The comparative genomic analysis data of SARS-CoV-2, based on biochemical and structural studies, demonstrate that SARS-CoV-2 two notable features, the first one is its binding to the human ACE2 receptor, and another one is regarding spike protein of SARS-CoV-2 that holds functional polybasic (furin) cleavage site at the S1-S2 periphery. It involves the incorporation of 12 nucleotides that ensued in possession of three O-linked glycans across the site (Fig. 2) [18-20]. The genetic data indisputably show that SARS-CoV-2 is not copied from any earlier used virus structure [21].
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Fig. (2). Descriptions of the spike protein of human SARS-CoV-2 and linked coronaviruses. (A) The red bar at the top of the figure showing spike protein that interacts with ACE2 receptor marked with blue boxes in both SARS-CoV-2 and related viruses. (B) Polybasic cleavage site and depiction of O-linked glycan residues in different organisms like a bat, pangolin, and human [17]. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

In the genome of coronaviruses, there is a receptor-binding domain (RBD) within the spike protein, which is the most flexible region in the entire genome [18]. There are around six amino acid residues that have been predicted to be significant for binding to ACE2 receptors and for establishing the host range of SARS-CoV-like viruses [22]. Structural and biochemical investigations confirmed that SARS-CoV-2 might have an RBD that interacts with a high affinity to ACE2 from humans, ferrets, cats, and other species considering the receptor homology [19, 20]. The high affinity of SARS-CoV-2 spike protein with human ACE2 is considered to be natural selection on a human or human-like ACE2 that allows another ideal partner for an interaction. Zhou et al. ascertained that SARS-CoV-2 engages the same ACE2 receptor to gain entry into the cell as SARS-CoV while the binding of SARS-CoV-2 is 10-20 times higher in affinity [18, 19].

Accumulating available data ascertains that SARS-CoV-2 is not the creation of purposeful operation or alterations. The two plausible conjectures proposed by Andersen et al. are (i) natural selection in an animal host before zoonotic transmission and (ii) natural selection in humans after zoonotic transmission [17]. The first case of SARS-CoV-2 appeared in November 2019 in the Hunan market at Wuhan, China, where tens of thousands of kilograms of animal flesh is sold for the general public consumption daily. Bats and pangolins naturally harbour more than 100 deadly viruses. The animals (bats and pangolin) are slaughtered in the market, and the virus might have transferred to humans after consuming it. Assuming the resemblance between SARS-CoV-2 and bat SARS-CoV, it is possible that bats assisted as reservoir hosts for its progenitor while humans may be the terminal host. SARS-CoV-1, MERS, and SARS-CoV-2 all were emerged from bats and were transferred to humans via the intermediate host.

3. INCUBATION PERIOD

Effective knowledge of the incubation period is essential for effective control and management of infection and formulation of the guidance to regulate further propagation. Several reports are available regarding the measurement of the incubation period based on the sample volume. Li et al. reported an incubation period of 5.2 days (95% confidence interval [CI], 4.1 to 7.0) based on 10 confirmed COVID-19 cases in Wuhan. The 95th percentile of the distribution of COVID-19 was 12.5 days (95% CI, 9.2-18) [23]. An early study conducted outside of Wuhan on 88 established cases calculated a mean incubation period of 6.4 days (95% credible interval: 5.6-7.7), ranging from 2.1-11.1 days [24]. Moreover, during the earlier outbreak phase, a study conducted
on 125 patients with well-defined exposure episodes revealed a median incubation period of 4.75 (interquartile range: 3.0-7.2) days [25]. However, when a large sample volume was used to estimate the incubation period, it came out to be only 3.0 days but may extend up to 24 days [26].

4. TRANSMISSION

As the earliest reports indicated that the direct exposure to the Huanan Seafood Wholesale Market of Wuhan was the primary mean of contracting the disease, researchers incorrectly concluded animal-to-human mode of transmission. When the number of cases evolved, this possibility was ruled out in favor of a new mechanism, i.e., human-to-human transmission. This mode of transmission considered both symptomatic and asymptomatic people as probable disease spreaders.

In a fashion similar to other respiratory viruses, the transmission of SARS-CoV-2 occurs primarily by droplet formation. Studies have shown that close interaction with symptomatic persons is necessary for viral transmission. However, recent findings suggest that the virus can survive on contaminated surfaces such as glass, plastic, copper cardboard for up to 24 hours and, in some cases, up to 2-3 days [27]. It is speculated that this novel virus doubles in 7 days, with the basic reproduction number (R₀ - R naught) being 2.2. The correlation study suggests that every patient spreads the infection to about 2.2 individuals. Importantly, the R of the SARS-CoV in 2002-2003 was ~3 [28].

4.1. Asymptomatic Transmission

A laboratory-confirmed COVID-19 positive person can harbor the pathogen without manifesting any signs and symptoms typical of the disease. These asymptomatic individuals may infrequently transmit the virus long before they eventually develop symptoms. Being asymptomatic does not warrant that no damage to the infected has occurred; it can still cause irreversible harm to the respiratory system. A recent article outlines the clinical patterns of asymptomatic infections. The researchers reported that test subjects exhibited mild signs of lung inflammation, akin to walking pneumonia, with no apparent symptoms of the COVID-19 [29]. Family members, healthcare professionals, colleagues, and persons in close contact with COVID-19 positive individuals comprise the most likely source of asymptomatic infections. Also, those people who have crossed paths with recently diagnosed or suspected patients must be treated as high-risk populations. Estimates of the proportion of asymptomatic cases have been reported at 16%, with a range from 6 to 41%. Thus, studies have reported 16.4% (in Hong Kong) [30], 17.9% (on the Diamond Princess Cruise Ship) [31], and up to 41.6% [32] asymptomatic ratio of COVID-19 patients. In another meta-analysis study, the pooled proportion of asymptomatic cases at the time of testing was estimated to be 25% [33]. The mode of transmission in the case of an asymptomatic person is still not clear. A study conducted in China analyzed the transmissibility of the asymptomatic cases, and it was found to be similar to that of symptomatic cases [34]. Additionally, they stated that asymptomatic cases might lead to only asymptomatic cases, citing the example of He et al. that reported the outbreak of SARS-CoV-2 on the Diamond Princess cruise ship. Recently, the number of asymptomatic cases was reported to fall within 6 to 41% of all confirmed COVID-19 cases [35]. It was also found that barely 8.4% of the persons remained strictly asymptomatic throughout the duration of the study, while most of them progressed to the symptomatic stage. A positive RT-PCR could only mean the potential transmissibility of the individual, thus highlighting the importance of analyzing the viral shedding patterns and live virus isolation. For a person to be truly infectious, the patient's RT-PCR level should be higher than a threshold value [36].

4.2. Symptomatic Transmission

While an asymptomatic person develops no signs and symptoms when infected with SARS-CoV-2, the symptomatic individual transmits infection while she/he is experiencing symptoms. Most of the published reports suggest that SARS-CoV-2 is mainly communicated by respiratory aerosol, by close direct contact with symptomatic persons, or through fomites [8, 37-40]. The virus is shed maximally in the upper respiratory tract during the initial onset of the infection [37, 41-43], i.e., within the first 3 days of the appearance of symptoms [33, 39]; and the peak viral load appears in the first week of disease development [44, 45]. Preliminary data suggest that symptomatic people can be more infectious as compared to those with later stages of the disease.

4.3. Pre-Symptomatic Transmission

Pre-symptomatic transmission is a type of transmission when the infected individual with no signs and symptoms transmits the virus and develops symptoms after 1-3 days. Several clusters of pre-symptomatic transmission have been identified through contact tracing [8, 46-48]. This is further supported by a report showing seven clusters of SARS-CoV-2 pre-symptomatic transmission [46]. Also, the proportion of pre-symptomatic transmission varied from 42.8% (39.8-45.9%) to 80.6% (78.1-83.0%) [49]. Thus, the probability that those infected with SARS-CoV-2 may possibly spread it before exhibiting disease indications, increasing the challenges associated with this disease.

As the COVID-19 pandemic continues to evolve, new evidence on the transmission of SARS-CoV-2 tends to accumulate. Viral particles have been reported in saliva, blood, urine, stool, and semen samples of the host [50-52]. Similar to other respiratory viruses, the spread of SARS-CoV-2 occurs via aerosol droplets. Close contact with a person coughing and sneezing is essential to acquire the disease. This means that the persons that are close to the carrier are more susceptible. As a result, the best way to control this epidemic is through social distancing and isolation. Recently, a new variant of SARS-CoV-2 emerged in the United Kingdom with a greater reproductive number and enhanced transmissibility [53].
5. RELATIONSHIP BETWEEN CHRONIC DISEASE AND COVID-19

Currently, there is a plethora of information available about COVID-19 patients that suggest that individuals over the age of 60 years with co-morbid conditions like cardiovascular, chronic pulmonary diseases, chronic kidney diseases, hepatitis B, hypertension, and some cancers are at greater risk of developing COVID-19 symptoms. In one of the studies by Tao Chen et al. it was reported that SARS-CoV-2 infection might cause both pulmonary & systemic inflammation, resulting in multi-organ failure, acute respiratory distress syndrome, respiratory failure, sepsis, acute cardiac injury, and heart failure in the patients, and ultimately they succumb to the infection [54].

6. THE IMMUNOLOGICAL PERSPECTIVE OF COVID-19

Elevated amounts of pro-inflammatory cytokines in serum, for example, IL-1B, IL-6, IL-12, IL-17, GM-CSF, IFNγ, IP10 (inducible protein 10), and MCP1 (monocyte chemotactrant protein 1), have been linked with pulmonary inflammation and widespread damage of lungs in SARS patients, while in MERS coronavirus infection, increased concentrations of IFNγ, TNFα, IL-15 and IL-17 were found [55, 56]. Huang C et al. reported that patients with SARS-CoV-2 infection also exhibited high amounts of IL1β, IFNγ and elevated T-helper (Th1) cell response. In the same study, they also compared some immunological parameters between ICU and non-ICU patients. Patients admitted with SARS-CoV-2 infection have elevated concentrations of GCSF, IP10, MCP1, MIP1A, and TNFα as compared to the non-ICU admitted patients [8]. Elevated levels of pro-inflammatory cytokines may cause shock and tissue damage in the heart, liver and kidney, respiratory failure and heart failure, etc.

It has been reported in previous studies that SARS-CoV-2 attacks patients with weakened immune responses. An effective immune response against SARS-CoV-2 is generally constituted by virus-specific cytotoxic T-cell (CTLs) and innate immune component natural killer (NK) cells [57]. The SARS-CoV-2 infection can activate both arms of immunity, i.e., innate and adaptive immune responses in the host. The COVID-19 patients possess a drastically reduced number of CD4+/ CD8+ T cells, B cells, and NK cells [8, 58-60]. The percentage of monocytes, eosinophils, and basophils too decreased significantly with the increase in neutrophil count [59, 61]. Studies have reported that patients who recovered either normally or through the convalescent plasma, the numbers of CD4+ T cells, CD8+ T cells, B cells, and NK cells normalize in them, and specific antibodies can also be detected [57, 62].

7. EFFECTIVE CONTAINMENT OF THE COVID-19 OUTBREAK

Infectious diseases are mainly controlled and eliminated once the route of transmission is cut off from the suspected patients to the normal population. Keeping in mind, there are four ways of person to person transmission of the virus, [i] droplet transmission comprising large respiratory droplets during cough & sneeze, [ii] aerosol transmission (cough or sneezes within the limited boundary), [iii] contact transmission (touching mouth, nose & eyes) and [iv] direct transmission (kissing and shaking hands). Transmission of SARS-CoV-2 may also arise through fomites in the immediate environment around the infected person [40].

In general, coronaviruses are sensitive to heat. In the laboratory, SARS-CoV-2 had been inactivated by incubation at 56 °C for 30 min. Few chemicals like ethanol (75%), peracetic acid, chlorine-based disinfectants can be used as a hand sanitiser to successfully deactivate the virus [18]. Few other possible ways of effective containment are (i) contact tracing from the confirmed positive patients, (ii) to know the spillover reservoir infection, (iii) identify community transmission, and (iv) testing of asymptomatic/mild cases.

7.1. Therapeutic Agents

As of September 2020, there is no FDA approved treatment for COVID-19; however, Russia claimed to have developed the first vaccine (Sputnik V) against SARS-CoV-2 before the effective clinical trial begins (https://sputnikvaccine.com). Experts across the globe raised considerable concern about the vaccine due to its safety and efficacy as the vaccine has not entered phase III clinical trial. Researchers have proposed various strategies to prevent further complications and organ damage and are limited to preventive & supportive therapies [63]. If the patients show some signs and symptoms of COVID-19, the antiviral drug administration may reduce infectiousness by reducing viral shedding in the respiratory secretions of patients. The antiviral treatment, prophylaxis, and their implementation have few requirements (safe treatments, minimum cost, and adequate supply). Several thousand clinical trials have been launched to conduct various tests against coronavirus treatments. Some of the clinical trials are based on repurposing and repositioning already existing drugs. Table 1 shows the current status of few drugs under the controlled trial and their status in different parts of the world.

Initially, the FDA has approved malaria drugs (chloroquine, hydroxychloroquine), although there is a meager chance of their action. However, a researcher from Oxford University conducted a randomized study on hydroxychloroquine against hospitalized COVID-19 patients and claimed no beneficial effect [64].

Keeping into consideration that members of the coronavirus family employ RNA as their genetic material, the researcher focused on RNA polymerase inhibition to kill the SARS-CoV-2 RNA polymerase enzyme that helps in copying a DNA sequence into an RNA sequence during the process of transcription. Various chemotherapeutic agents such as Remdesivir, 5-flourouracil, ribavirin, and favipiravir have been widely acclaimed to block the virus's proteins from making copies of the virus. It has been postulated that a combination of four drugs can be used for the treatment of COVID-19.
Table 1. Some of the drugs are under investigation (clinical trials) to combat COVID-19 under the strategy of drug repurposing or drug repositioning.

<table>
<thead>
<tr>
<th>S. No</th>
<th>Name of Drug</th>
<th>Nature of Drug</th>
<th>Mechanism of Action</th>
<th>Name of Disease</th>
<th>Brand Name</th>
<th>Manufacturer</th>
<th>Clinical Trial (Phase)</th>
<th>References</th>
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<tbody>
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<td>1.</td>
<td>Remdesivir</td>
<td>Antiviral</td>
<td>Inhibits RNA de-</td>
<td>Ebola virus</td>
<td>Veklury®</td>
<td>Gilead Sciences</td>
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<td>[66]</td>
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<td></td>
<td></td>
<td>pendent RNA poly-</td>
<td>and Marburg virus Infection</td>
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<td>Antiretroviral</td>
<td>Protease Inhibitor</td>
<td>Treatment of HIV</td>
<td>Kaletra</td>
<td>Hoffman-La Roche and Chugai</td>
<td>IV</td>
<td>[67]</td>
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<td>Tocilizumab/Altizumab</td>
<td>Immunosuppressive</td>
<td>Act on IL-6R</td>
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<td>Regeneron Pharmaceuticals &amp; Sanofi</td>
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<td>[68]</td>
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<td>Influenza</td>
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<td>FUJIFILM Toyama</td>
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<td>[69-70]</td>
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<td>Tamiflu</td>
<td>Roche</td>
<td>II/III</td>
<td>[71]</td>
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<td>Pfizer</td>
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<td>Roche</td>
<td>II/III</td>
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<td>Reduces fibroblast proliferation &amp; inhibits TGF-1</td>
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<td>Pirespa</td>
<td>Marnac, Inc</td>
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<td>Novartis</td>
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<td>[83]</td>
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<td>Immunomodulatory</td>
<td>Stimulating T cells &amp; decreasing TNF-a production</td>
<td>Multiple myeloma</td>
<td>Contergan</td>
<td>CIBA</td>
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<td>[84]</td>
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<td>Antiretroviral</td>
<td>Non-peptidic inhibitor of protease, Inhibits CytP450</td>
<td>HIV/AIDS</td>
<td>Prezista, Tybost</td>
<td>Tibotec, Gilead Sciences, Inc./Shanghai Public Health Center</td>
<td>III completed</td>
<td>[85]</td>
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<td>Blocks TLR4</td>
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<td>[86]</td>
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<td>Pacritinib</td>
<td>Antineoplastic</td>
<td>Inhibitor of Janus Kinase 2 (JAK2)</td>
<td>Acute Myeloid Leukemia</td>
<td>N/A</td>
<td>CTI BioPharma Corp</td>
<td>III</td>
<td>[87]</td>
</tr>
<tr>
<td>20.</td>
<td>Baricitinib</td>
<td>Antiinflammatory and antiviral</td>
<td>A potent and selective inhibitor of JAK</td>
<td>Rheumatoid arthritis</td>
<td>N/A</td>
<td>Eli Lilly and Co</td>
<td>III</td>
<td>[88]</td>
</tr>
<tr>
<td>21.</td>
<td>Dapagliflozinpropanediol</td>
<td>Antidiabetic</td>
<td>Inhibitor of glucose transporter</td>
<td>Type 2 diabetes mellitus</td>
<td>FARXZIA</td>
<td>AstraZeneca Plc</td>
<td>III</td>
<td>[89]</td>
</tr>
<tr>
<td>22.</td>
<td>Immune globulin (human)</td>
<td>Sterilized human plasma</td>
<td>Improves hypoxia</td>
<td>Improves hypoxia</td>
<td>Congenital agammaglobulinemia</td>
<td>Octagam R 10%</td>
<td>Serum Institute of India Ltd.</td>
<td>III</td>
</tr>
<tr>
<td>23.</td>
<td>VPM-1002</td>
<td>Antiviral and immune-modulatory</td>
<td>BCG vaccine</td>
<td>TB, Childhood immunization</td>
<td>N/A</td>
<td>Serum Institute of India Ltd.</td>
<td>III</td>
<td>[91]</td>
</tr>
</tbody>
</table>
Ribavirin has been used to treat HCV, while favipiravir was approved as an anti-influenza drug in Japan. It has been approved for treating COVID-19 in China and Italy. The researchers have also thought of targeting the main SARS-CoV-2 enzyme for splitting proteins, known as the main protease (Mpro). The involved drug might play a key role in mediating viral replication. This is an attractive drug target for this virus, and humans do not naturally have this enzyme.

Some indigenous drugs like Ashwagandha and Propolis can offer some preventive or even therapeutic value, according to a recent study by Kumar et al. [65]. It stated that although these are easily available and affordable, one has to be cautious about the content of bioactive ingredients.

7.2. Mechanism of Action of Anti-COVID-19 Drugs

ACE2 receptor, present on the surface of target cells, binds to the coronavirus to facilitate its entry to the cell. A viral molecule modifies ACE2 so that virus can bind to the cell. The high level of ACE2 in the lungs play a crucial role in the progression of lung disorders related to COVID-19. The ACE2 is more abundant in males as compared to their female counterparts. This explains the reason why males are more susceptible to SARS-CoV-2 infection as compared to females. Besides the lungs, the ACE2 is also found in the heart and kidney cells and also in the tissue lining of blood vessels. Interestingly, ACE2 is more abundant in the testes and might partially explain why males are more susceptible to SARS-CoV-2 infection.

Keeping into consideration the fact that the ACE2 receptor is the first contact point of virus for its entry into the host cell, any strategy that inhibits or checks this interaction will lead to the development of a potent anti-viral agent. The neutralizing antibody developed in the healthy immune individual also works on the same strategy, as they do not allow the invading virus to interact with the ACE2 receptor. Thus, inhibitors that can compete with the virus to bind with ACE2 may emerge as potent drug molecules against SARS-CoV-2.

Remdesivir, one of the centre-stage drugs, is commonly used for the current treatment of COVID-19 under drug repurposing and drug regrouping program. Due to its antiviral properties, it has shown promising effects on MERS and SARS previously; therefore, its testing for the COVID-19 is also underway. Remdesivir is a RNA-dependent RNA polymerase inhibitor and evades proofreading by viral exonuclease, thereby reducing viral RNA production. The nucleoside analog has been extensively used for SARS-CoV-2 infection as it ceases to premature termination of RNA chains [95].

Lopinavir/Ritonavir combination is under clinical trials in various countries due to its protease inhibition function, which ultimately blocks viral replication. Lopinavir appears to be the agent, which interacts with the virus, while ritonavir is an inhibitor of CYP3A, works mainly to diminish the metabolism of lopinavir, hence improving the levels of lopinavir. A recent cohort study on lopinavir/ritonavir reported by Young et al. suggested that the combination of lopinavir/ritonavir alone was not predominantly notable. For future clinical trials, triple therapy with lopinavir/ritonavir/ribavirin might be explored based on previous experiments [96].

Sarilumab is a monoclonal antibody that functions by inhibiting the IL-6 pathway through interacting and blocking the IL-6 receptor. Scientific evidence appeared to imply that sarilumab may be a critical management choice for patients suffering from COVID-19. IL-6 is connected with an intense inflammatory reaction in the lungs of severely and critically ill COVID-19 patients. Regeneron&Sanofi pharmaceuticals have initiated a clinical development to treat hospitalized patients with severe coronavirus infection in multi-centre, double-blind, phase III trial. Tocilizumab is another humanized immunosuppressive monoclonal antibody that mainly targets the IL-6 receptor. Tocilizumab interacts with both soluble and membrane-bound IL-6 receptors. The interaction blocks IL-6 from exerting the downstream pro-inflammatory effect. The competitive inhibition of IL-6/IL-6 receptor binding occurs as tocilizumab recognizes binding sites on both receptor forms.

Favipiravir is another RNA-dependent RNA polymerase inhibitor, which is capable of preventing the replication of several RNA viruses like flav-, alpha-, filo-, bunya-, arena-, and noro-viruses [97]. Once inside the cell, the favipiravir is converted into active phosphorylated components and is accepted as a substrate by viral RNA polymerase, consequently inhibiting RNA polymerase activity [98]. In one of the controlled drug trial studies by Dong et al. it has been shown that favipiravir is more efficient as compared to lopinavir/ritonavir combination while managing the COVID-19 patients having lesser side effects [99].

Ribavirin is an antiviral drug and is a guanosine analogue that has been extensively applied in the treatment of severe acute respiratory syndrome as monotherapy as well as combined therapy (lopinavir/ritonavir). Patients cured with combined therapy had shown less possibility of acute respiratory distress syndrome and death [100]. The basis of anti-viral activity lies in the fact that ribavirin hinders the replication mechanism in viruses possessing the RNA as well as DNA genome. The structure of ribavirin affects RNA capping that depends on natural guanosine to inhibit RNA degradation and destabilize viral RNA. Also, ribavirin interferes with natural guanosine generation by directly preventing inosine monophosphate dehydrogenase, the pathway crucial for the assembly of the guanosine precursor to guanosine [101].

Umifenovir (Arbidol) is a broad-spectrum antiviral drug developed for the prophylaxis and treatment of influenza A&B. Arbidol is indicated to be functional against many DNA/RNA and enveloped/non-enveloped viruses [102]. The principal mechanism of action of arbidol is to establish intercalation into membrane lipids, thereby causing an alteration in the membrane fusion and virus particles [103]. The immunomodulatory, antiviral capability of arbidol has been widely exploited for the management of human viral infections such as SARS-CoV-2.
Ivermectin is an anti-parasitic drug approved by FDA and is widely used against dengue fever, HIV, influenza, and Zika virus. The mechanism through which ivermectin targets SARS-CoV-2 is still mysterious; however, it is thought to be similar to how it functions on other viruses, i.e., preventing the virus from dampening down the host cell’s ability to clear it. It has been reported that ivermectin has broad-spectrum anti-SARS-CoV-2 activity in vitro [79].

The FDA granted “fast track” clearance to Leronlimab, a CCR5 antagonist, for initiation and enrollment of the clinical trial for severely ill patients infected with SARS-CoV-2 [104]. Leronlimab targets the CCR5 receptor, which is a protein situated on the surface of several cells comprising white blood cells and cancer cells. CytoDyn (developer of leronlimab) continues to claim that there is an increase in the profoundly decreased CD8 T lymphocyte percentages by day 3. The standardized ratio of CD4/CD8 and the production of cytokine-like IL-6 continue to improve in patients undergoing treatment with leronlimab in the clinical trial.

Tenofovir disoproxil fumarate (a prodrug of tenofovir) is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. In an initial reaction, tenofovir disoproxil fumarate hydrolyzes to form tenofovir and ensues a phosphorylation reaction that leads to the formation of tenofovir-diphosphate by cellular enzymes. Tenofovir diphosphate selectively impedes the activity of HIV-1 reverse transcriptase by competing with the biological substrate deoxyadenosine 5’-triphosphate and, after integration into DNA, by DNA chain termination. After integration into the growing DNA strand, the drug causes early termination of DNA transcription, thereby stopping viral replication.

Pirfenidone is a broad-spectrum anti-inflammatory and anti-fibrotic drug that exhibits inhibitory fibrosis progression in animal models as well as in idiopathic pulmonary fibrosis patients. Conte et al. reported that pirfenidone considerably hindered the proliferation of fibroblast and decreased TGF-β-induced α-SMA and Col-I expression at both mRNA and protein levels [105]. Furthermore, pirfenidone controls HLF proliferation and TGF-β mediated differentiation into myofibroblasts at the same time fibrogenic activity by inhibiting key TGF-β-induced signalling pathway’s activation. Neuraminidase enzyme expressed by the viral surface stimulates the release of virus from infected cells and assists viral movement within the respiratory tract. Oseltamivir inhibits neuraminidase enzyme causing virions to stay attached to the infected cells, and these also get entrapped in respiratory discharges [106].

7.3. Repurposing of Existing Antivirals

Drug re-profiling or repositioning involves the identification of existing drugs and their subsequent use as an effective therapeutic agent against novel coronavirus disease. Broad-spectrum antiviral agents (BSAAs) can be contemplated as suitable drug repurposing candidates to treat SARS-CoV-2 infection. The promiscuity of the replicative mechanism of virus and host interactions offer prospective targets that can be employed for the development of effective antivirals. The antiviral combinations offer a novel perspective with a ‘double hit effect’ to find a successful strategy against this important virus.

Keeping into consideration the fact that the virus can transfer its genetic material by the membrane of the virus with that of the host cell plasma membrane. Thus a membrane fusion inhibitor like umifenovir can be employed to check the transfer of viral genetic material to the host cell. Similarly, drugs such as lopinavir/ritonavir can target viral protease, thereby check the establishment of the virus in the host. Both lopinavir/ritonavir has been permitted for the management of Influenza and HIV.

Remdesivir is a viral RNA-dependent RNA polymerase inhibitor that can also inhibit coronaviridae family members, including SARS-CoV-2. Remdesivir has been reported to exhibit remarkable killing of the Ebola virus. The drug has been presented to act at entry and post-entry phases of the SARS-CoV-2 infection. A recently computational study has shown an effective way to control SARS-CoV-2 infection with existing drugs like remdesivir, lopinavir, and theophylline [107].

7.4. Vaccine Strategies Against COVID-19

In order to develop an effective prophylactic strategy against this deadly virus, it is imperative that the as-developed vaccine should not only offer protection rather it should also impart a long-term immune response in the host. Long-term protection can be accomplished by exposure to coronaviruses using vaccination. Although some multinational pharmaceutical giants like Janssen, Sanofi, Pfizer, and GlaxoSmithKline are engaged in developing a vaccine against COVID-19, the race is led by a majority of small vaccine manufacturers with little experience in large-scale vaccine production. Most of the vaccine developers belong to private institutions or industries, while a few remaining academic or non-profit organizations are also involved. Therefore, this necessitates the need for global coordination in the manufacturing and supply of vaccine candidates to meet the worldwide demand. Lead developers of active COVID-19 vaccine candidates are found in only 19 countries, accounting cumulatively for over three-quarters of the global population [108].

Because of its viral background and also severe lethality issues, it is a very arduous task to develop a safe and effective vaccine against COVID-19 shortly. Although, there are reports that claim the development of effective vaccines that impart protection when tested in vitro. A researcher from the National Institute of Allergy and Infectious Disease has initiated a phase III clinical trial of mRNA-1273 (a novel lipid nanoparticle encapsulated mRNA) based vaccine that determines the full length, perfusion stabilized spike protein of SARS-CoV-2 in collaboration with Moderna, Inc., pharmaceutical company [109]. A novel vaccine candidate (mRNA-1273) has been reported to induce elevated levels of binding antibodies in the immunized subjects. The level of the neutralizing antibodies was found to be much higher and even sometimes found to supersede the levels seen in the
blood serum of the patients who had recently recuperated from COVID-19. The as-developed vaccine was not only safe and well-tolerated, but only two or three participants also experienced flu-like symptoms after receiving a second vaccination at a 250 microgram dose.

WHO (August 13, 2020) has released a list of candidate vaccines, where a total of 29 candidate vaccines are in clinical assessment while more than 130 are in the stage of preclinical testing in various parts of the world (DRAFT landscape of COVID-19 candidate vaccines [110]. In Table 2, we have summarized a few of the candidate vaccines that are in the clinical/pre-clinical trial stage. There are unprecedented involvement and efforts across the globe to develop an effective vaccine against SARS-CoV-2. Normally any vaccine to come up in the market for clinical use takes around 10-15 years of rigorous practice in various stages to cross. Within the two months of a viral epidemic, the genetic sequence was made available to work on the development of effective diagnostic and prophylactic measures. The candidate vaccines comprised a different vaccine design, including whole DNA, RNA, killed virus, subunit, attenuated, viral vector, liposome-encapsulated and plant-based products.

The ChAdOx1 nCoV-19 based vaccine trials had claimed that the vaccine activates rhesus macaque monkeys' immune systems to eradicate the lethal virus [111, 112]. There was a significant reduction in the viral load in the bronchoalveolar lavage fluid and respiratory tract tissue in the animal vaccinated with SARS-CoV-2 with respect to control animals. The success of the vaccine encouraged the involved researcher for the subsequent human trials, but specialists cautioned that it remains to be realized if it is as effective in humans. As specified in Table 2, it is anticipated that several ongoing human trials will help us in the procurement of an effective vaccine against this particular disease in the near future. Inactivated whole-virus vaccine comprising the virion after inactivation (either by heat or chemical) is also under investigation for a vaccine against SARS-CoV-2. It possesses several native antigenic components capable of inducing assorted immunologic reactions against the pathogen.

One of the most immunogenic vaccines that do not need an adjuvant to boost an ideal immune response is Live-Attenuated Vaccines (LAV). This may be due to its usefulness to provide an effective immune response, mimicking the natural course of infection as it contains viable, low virulent but an attenuated live virus that is incapable of disease production in a normal healthy individual. They replicate gradually and thus provide a sustained amount of antigen for a long period after a single immunization, reducing the need for a booster dose [113]. Currently, numerous pharmaceutical firms acquired virus strains (SARS-CoV-2) and commenced significant vaccine development. Subunit vaccines contain antigenic determinants with high immunogenicity. They are safe and easily manufactured by recombinant DNA technology, although requiring an adjuvant to boost immune response. Most of the research on subunit vaccines rely on the use of spike glycoprotein S and its fragments, such as S1, S2, RBD, and nucleocapsid protein as prime target antigens [114].

DNA-based vaccines (DVs) carry the desired antigenic gene into a plasmid, which is then delivered into the host that translates the antigenic protein, thus stimulating the immune system in a way similar to its natural course of infection. DVs elicit both the cell-mediated and humoral immune system. They are very stable and can be procured in a short period as they do not require a culture of the virus. Several DVs candidates encode the S protein of the S1 domain to thwart interaction to the human ACE2 receptor, a receptor necessary for viral entry.

### 7.5. Plasma Therapy

Plasma therapy is in clinical use since the Spanish pandemic flu in 1918, in which almost 30% of the world population became ill, and 50 million people expired [132]. Convalescent human plasma may have efficacy in the management of a plethora of diseases like rabies, measles, hepatitis B, cytomegalovirus, respiratory syncytial virus, and SARS [133-135]. When first-time convalescent plasma was given to only five critically ill patients for the treatment of COVID-19, it was found that three patients recovered while two came in stable condition post 37 transfusions of plasma [136].

Convalescent plasma therapy has been utilized as an option to progress the survival rate of COVID-19 patients whose ailments continue to decline, notwithstanding treatment with methylprednisolone, remdesivir, and other available antiviral drugs. Considering the fact that post-exposure to SARS-CoV-2, the recovered patients harbor a great deal of neutralizing antibodies that behold a strong tendency to either neutralize invading virus particles or compete with them to interact with ACE2 protein found on the surface of target cells. Considering this fact, convalescent plasma from the patients who have recovered from SARS-CoV-2 infection has been widely utilized as a treatment without the occurrence of severe effects. It will be meaningful to test the safety as well as the efficacy of convalescent plasma transfusion in SARS-CoV-2 infected patients.

Research-based current clinical findings suggest that convalescent plasma therapy should be applied to SARS-CoV-2 infected patients with the right phase or severity at the right time. It is a well-known fact that most mild (infection) SARS-CoV-2 patients can be self-recovered, and convalescent plasma therapy may not be appropriate for them. For critically ill end-stage SARS-CoV-2 patients, convalescent plasma therapy may not be able to regress the poor outcomes as reported by Zeng et al. [137].

### 7.6. Future Perspective

The effectiveness of the drug repurposing strategy depends on the fact that whether such agents would evolve as a virus-specific vaccine or small molecules that will ensue in the development of the gold standard modern anti-SARS-CoV-2 campaign. Taking a cue from the knowledge of meticulous oncology, where targeted cancer therapies, as
Table 2. List of some of the vaccines that are under controlled trials in the USA, Europe, and other parts of the world. Some of the vaccines are in the mentioned respective stages.

<table>
<thead>
<tr>
<th>S. No</th>
<th>Name of Vaccine</th>
<th>Nature of Vaccine</th>
<th>Name of the Disease</th>
<th>Manufacturer</th>
<th>Clinical Trial (Phase)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Non-replicating viral vector</td>
<td>Adenovirus type 5 vector</td>
<td>COVID-19, Ebola</td>
<td>CanSino Biological Inc./Beijing Institute of Biotechnology</td>
<td>Phase III</td>
<td>[115, 116]</td>
</tr>
<tr>
<td>2</td>
<td>DNA</td>
<td>DNA plasmid vaccine electroproporation device</td>
<td>COVID-19, Lassa, Ni-pah, HIV, Filovirus, HPV, Zika, Hepatitis</td>
<td>Inovio Pharmaceuticals</td>
<td>Phase I</td>
<td>[117]</td>
</tr>
<tr>
<td>3</td>
<td>RNA</td>
<td>LNP encapsulated mRNA</td>
<td>Multiple candidates, COVID-19</td>
<td>Moderna/NIAID</td>
<td>Phase III</td>
<td>[118]</td>
</tr>
<tr>
<td>4</td>
<td>DNA</td>
<td>DNA with electroproporation</td>
<td>COVID-19</td>
<td>Karolinska Institute/Cobra Biologics (OPENCORONA Project)</td>
<td>Pre-clinical</td>
<td>[119]</td>
</tr>
<tr>
<td>5</td>
<td>DNA</td>
<td>Plasmid DNA, Needle-Free Delivery</td>
<td>COVID-19, SARS</td>
<td>Immunomic Therapeutics, Inc./EpiVax, Inc./Pharmajet, Inc.</td>
<td>Pre-clinical</td>
<td>[120]</td>
</tr>
<tr>
<td>6</td>
<td>Inactivated</td>
<td>Inactivated + Alum</td>
<td>COVID-19, SARS</td>
<td>Sinovac</td>
<td>Phase III</td>
<td>[121]</td>
</tr>
<tr>
<td>7</td>
<td>Live attenuated virus</td>
<td>Deoptimized live attenuated vaccines</td>
<td>COVID-19, HAV, Influenza, ZIKV, FMD, SIV, RSV, DENV</td>
<td>Codagenix/Serum Institute of India</td>
<td>Pre-clinical</td>
<td>[122]</td>
</tr>
<tr>
<td>8</td>
<td>Non-replicating viral vector</td>
<td>ChAdOx1</td>
<td>COVID-19, MERS, TB, Chikungunya, Zika, Plague, MenB, Influenza</td>
<td>Univ. of Oxford, licensed to AstraZeneca</td>
<td>Phase III</td>
<td>[123]</td>
</tr>
<tr>
<td>9</td>
<td>Non-replicating viral vector</td>
<td>MVA encoded VLP</td>
<td>COVID-19, LASV, Ebola, HIV</td>
<td>GeoVax/BravoVax</td>
<td>Pre-clinical</td>
<td>[124]</td>
</tr>
<tr>
<td>10</td>
<td>Protein Subunit</td>
<td>Capsid-like particle</td>
<td>COVID-19</td>
<td>AdaptVac (PREVENT-nCoV consortium)</td>
<td>Pre-clinical</td>
<td>[125]</td>
</tr>
<tr>
<td>11</td>
<td>Protein Subunit</td>
<td>S protein</td>
<td>COVID-19</td>
<td>WRAIR/USAMRIID</td>
<td>Pre-clinical</td>
<td>[126]</td>
</tr>
<tr>
<td>12</td>
<td>Protein Subunit</td>
<td>Microneedle arrays S1 subunit</td>
<td>COVID-19, MERS</td>
<td>Pre-clinical</td>
<td>Pre-clinical</td>
<td>[126]</td>
</tr>
<tr>
<td>13</td>
<td>Protein Subunit</td>
<td>Peptide</td>
<td>COVID-19</td>
<td>Vaxil Bio</td>
<td>Pre-clinical</td>
<td>[124]</td>
</tr>
<tr>
<td>14</td>
<td>Protein Subunit</td>
<td>VLP-recombinant protein nanoparticle vaccine + Matrix M</td>
<td>COVID-19, RSV, HPV, EBOV, VZV</td>
<td>Novavax</td>
<td>Phase Ib</td>
<td>[124]</td>
</tr>
<tr>
<td>15</td>
<td>Protein Subunit</td>
<td>Molecular clamp stabilized spike protein with MF59 adjuvant</td>
<td>COVID-19, Nipah, Influenza, Ebola, Lassa</td>
<td>Univ. of Queensland/CSL/Seqirus</td>
<td>Phase I</td>
<td>[127]</td>
</tr>
<tr>
<td>16</td>
<td>Protein Subunit</td>
<td>S1 or RBD</td>
<td>COVID-19, SARS</td>
<td>Baylor college of Medicine</td>
<td>Pre-clinical</td>
<td>[128]</td>
</tr>
<tr>
<td>17</td>
<td>Protein Subunit</td>
<td>Subunit protein, plant produced</td>
<td>COVID-19</td>
<td>iBio/CC-Pharming</td>
<td>Pre-clinical</td>
<td>[124]</td>
</tr>
<tr>
<td>18</td>
<td>Protein Subunit</td>
<td>COVID-19 XWG-03 truncated S (spike) proteins</td>
<td>COVID-19, HPV</td>
<td>Innovax/Xiamen Univ./GSK</td>
<td>Pre-clinical</td>
<td>[124]</td>
</tr>
<tr>
<td>19</td>
<td>Replicating Viral vector</td>
<td>Measles Vector</td>
<td>COVID-19, West Nile, Chikungunya, Ebola, Zika, Lassa</td>
<td>Institute Pasteur/Themis/Univ. of Pittsburgh center for vaccine research</td>
<td>Phase I</td>
<td>[129]</td>
</tr>
<tr>
<td>20</td>
<td>Live attenuated virus</td>
<td>Measles virus (S, N targets)</td>
<td>COVID-19, Zika, H7N9, Chikungunya</td>
<td>DZIF-German Center for Infection Research</td>
<td>Phase I</td>
<td>[130]</td>
</tr>
<tr>
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<td>RNA</td>
<td>LNP-encapsulated mRNA</td>
<td>COVID-19, MERS</td>
<td>Univ. of Tokyo/Daichi-Sankyo</td>
<td>Pre-clinical</td>
<td>[131]</td>
</tr>
<tr>
<td>22</td>
<td>RNA</td>
<td>Liposome-encapsulated mRNA</td>
<td>COVID-19</td>
<td>BIOCAD</td>
<td>Pre-clinical</td>
<td>[124]</td>
</tr>
<tr>
<td>23</td>
<td>RNA</td>
<td>mRNA</td>
<td>COVID-19</td>
<td>China CDC/Tongji Univ./Stermina</td>
<td>Pre-clinical</td>
<td>[124]</td>
</tr>
<tr>
<td>24</td>
<td>VLP</td>
<td>Virus-like particle, based on RBD displayed on virus-like particles</td>
<td>COVID-19</td>
<td>Saiba GmbH</td>
<td>Pre-clinical</td>
<td>[124]</td>
</tr>
<tr>
<td>25</td>
<td>VLP</td>
<td>ADDomer TM multiepitope display</td>
<td>COVID-19</td>
<td>Imophoron Ltd &amp; Bristol Univ. Max Planck Center</td>
<td>Pre-clinical</td>
<td>[124]</td>
</tr>
</tbody>
</table>

VLP= Virus-like particle.

Promiscuous Biological Features of Newly Emerged SARS-CoV-2

The nature of vaccines is in the Table.

As immunotherapeutics have made a mark towards cancer, the development of a broad-spectrum approach will be a prime focus while dealing with the SARS-CoV-2. Notably, the absence of specificity of BSAs may better be associated with the appearance of drug resistance and new virulent forms. For instance, nsp14-ExoN, in addition to its cofactor nsp-10, coronavirus possess the property to repair nucleotide mismatch produced by nucleoside analogs like ribavirin, therefore possibly opposing the antiviral effect of BSAs [138]. In fact, effective measures have to be taken to control the ability of SARS-CoV-2 to conserve its genomic integrity. However, it should be done in the line to permit the virus a certain degree of evolutionary freedom to mutate. Here high-throughput screening can come to the rescue. Chemical
entities possessing an affinity against nsp14-ExoN catalytic subunit or those with allosteric properties at important sites with conserved residues producing conformational rearrangement of the whole RNA repair complex will tremendously help in the identification of viral nuclease inhibitor. Interestingly, the drug repurposing should be comprehensive with the structure-based strategy of preventative/therapeutic vaccines. The toxicity issues should also be kept in mind in formulating the vaccine development of small molecules. Complete analysis of SARS-CoV-2 spike glycoprotein has now been deciphered at atomic resolution. Hopefully, the detailed atomic information may spur rapid efforts in the development of effective vaccines. However, such processes are time-bound and can be delayed by the prospective blunted antigenicity (epitopes) and genetic drift of SARS-CoV-2 [139]. One of the critical points in the hunt for drug repurposing is the issue of patent protection as per national/international guidelines hampering the smooth findings. A universal health tragedy of this extent needs an audacious, exhaustive approach at national/international and political fronts. Both scientists and government monitoring bodies should come forward with new as well as old existing compounds to cure the infection. The urgently launched clinical trials worldwide on investigational medicinal products for the current COVID-19 outbreak should read out at the earliest possible period. We can anticipate the notion of drug repurposing for emerging viral diseases to be scrutinized based on these results.

CONCLUSION

The novel SARS-CoV-2 coronavirus, first reported in the city of Wuhan, China, in the first week of December 2019, inflicted a pandemic to 191 countries worldwide. The newly evolved virus has been classified as a product of natural evolution. There is a strong conundrum that the virus had been engineered purposely or accidentally by a group of researchers. However, the evaluation of public genome sequence data from SARS-CoV-2 and related viruses has rescinded any such possibility that the virus was made in a laboratory or otherwise engineered. Within a few weeks of the epidemic, scientists from China sequenced the complete genome of SARS-CoV-2, and the data was put into the public domain. The sequenced data displayed that COVID-19 cases augmented due to human transmission after a particular infection introduced into the human population. The spike protein analysis suggests two important findings, (i) the RBD, a structure perceived as a hook that holds onto host cells, and (ii) cleavage site, function as a molecular opener that permits the virus to break open and gain entry into host cells. The RBD portion of the SARS-CoV-2 spike proteins effectively targets a molecular feature on the human cells called ACE2, a receptor involved in regulating blood pressure. The binding of SARS-CoV-2 spike protein with the ACE2 receptor is so effective that it compels us to conclude that it was the result of natural selection and not the product of genetic engineering. Coronaviruses are a large family of viruses that can cause illness, ranging widely in severity. The first known coronavirus illness emerged as a SARS epidemic in China in the year 2003. A second outbreak of illness was reported in 2012 in the Kingdom of Saudi Arabia and the middle east (MERS).

In India, the Indian Council of Medical Research, in its supervision for the proper recording of COVID-19 casualties, postulates that deaths with suspected coronavirus symptoms will be recorded as “probable COVID-19” fatalities. Fatalities, where tests are anticipated with the presence of signs, will be counted as suspected casualties. The patients whose test underwent negative but have symptoms will be treated as clinically-epidemiologically diagnosed COVID-19. Detailed data is required from rural areas on a district basis for each of the states in India. This will help to assess the impact of SARS-CoV-2 infection on community health. This, in turn, will help in appropriate planning whereby timely interventions will help in the protection of communities.

However, there are still many valid queries that remain to be answered and explained in due course of time. The relationship between SARS-CoV-2 infection and animal cause the disease has not yet been verified by animal experiments to ascertain Koch’s postulates. Future research should emphasize active surveillance of SARS related coronaviruses, considering its outbreak and lethality in mankind. The recent report regarding the emergence of various new mutants of the virus has further complicated the whole threat. Because of the RNA-based genome, the virus has error-prone genetic events that may lead to antigenic drift and shift, making the whole preventive process more complex.

Finally, broad-spectrum antiviral drugs and vaccines should be examined and developed worldwide against emerging infectious diseases in the future. Strict regulation for domestic animal and wildlife consumption needs to be implemented, keeping in mind the outbreak of infectious diseases. The outbreak of coronaviruses that have generally been perceived as SARS-related coronaviruses could cause future disease if not analysed properly this time [18]. SARS-CoV-2 infection is posing a major life-threatening challenge to the contemporary world. Considering all the facts, the elimination of SARS-CoV-2 can be done once the source of infection, prevention of route of transmission, protecting the susceptible population, and their early diagnosis can be achieved. To fight against this lethal COVID-19, the synchronic efforts of clinical, medical, paramedical, public health, and basic research staff need to be made.

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CONFLICT OF INTEREST

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