Review

Current Understanding of Novel Coronavirus: Molecular Pathogenesis, Diagnosis, and Treatment Approaches

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Abstract: An outbreak of "Pneumonia of Unknown Etiology" occurred in Wuhan, China, in late December 2019. Later, the agent factor was identified and coined as SARS-CoV-2, and the disease was named coronavirus disease 2019 (COVID-19). In a shorter period, this newly emergent infection brought the world to a standstill. On 11 March 2020, the WHO declared COVID-19 as a pandemic. Researchers across the globe have joined their hands to investigate SARS-CoV-2 in terms of pathogenicity, transmissibility, and deduce therapeutics to subjugate this infection. The researchers and scholars practicing different arts of medicine are on an extensive quest to come up with safer ways to curb the pathological implications of this viral infection. A huge number of clinical trials are underway from the branch of allopathy and naturopathy. Besides, a paradigm shift on cellular

therapy and nano-medicine protocols has to be optimized for better clinical and functional outcomes of COVID-19-affected individuals. This article unveils a comprehensive review of the pathogenesis mode of spread, and various treatment modalities to combat COVID-19 disease.

1. Introduction

The city of Wuhan in China witnessed an outbreak of pneumonia caused by a novel coronavirus in the late winter of December 2019, and with a rampant spread throughout China, it periled the world to emerge as a pandemic [1]. The etiological agent of the disease was originally called as 2019 novel coronavirus (2019-nCoV), but later it was named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease process as Coronavirus Disease–2019 (COVID-19) by the WHO [2]. Later, SARS-CoV-2 was declared an International Public Health Emergency by the WHO on 30th January 2020. As of 14th March 2021, the world has encountered 120 million confirmed cases and 2.6 million deaths reported among them (source: Worldometer, www.worldometers.info). The transmitting capacity of SARS-CoV-2 is beyond that of its ancestral SARS-CoV that caused an outbreak of SARS in 2003 [3]. The escalation in the number of confirmed COVID-19 cases forecasts the prevailing scenarios gloomily and warrants stringent preventive and control measures. The clinical spectrum and manifestations involve the respiratory system undergoing the major brunt of COVID-19 infection; however, damage to the cardiovascular system has been reported by some patients [4]. Some patients with existing cardiovascular diseases (CVDs) may have a higher risk of associated mortality. Therefore, it is equivalently important to understand the mechanisms and extent of damage to the cardiovascular system by SARS-CoV-2 infectivity and come up with an effective treatment for these patients while minimizing the associated mortality.

Currently, there is no definite antiviral therapy developed for treating SARS-CoV-2 infection. The mainstay of treatment is rendering supportive care, as per the presenting complaints of the patient. Even treating with a combination of recombinant Interferon (IFN) and Ribavirin has been reported to show limited response against SARS-CoV-2 infection [5,6]. Following the episodes of SARS and MERS epidemics, persistent efforts have been made in streamlining newer antiviral agents to target the viral proteases, polymerases, MTases, and entry proteins respectively. However, none proved to be fruitful in terms of effectivity during the clinical trials [7–9]. With the flattening of the COVID-19 curve of infectivity, immunotherapies involving plasma and antibodies procured from convalescent patients have been proposed to address the present circumstances [10]. Besides, various vaccine strategies involving utilization of inactivated viruses, live-attenuated viruses, viral vector-based vaccines, subunit vaccines, recombinant proteins, and DNA vaccines have been evaluated in animals and are emerging as a preventable strategy [11,12]. Due to the lack of traditional licensed treatment or vaccine, the infection mandates implementation of infection control measures with establishing an early diagnosis, reporting, isolation, and rendering supportive treatments effectively. Individualized efforts by inculcating the healthy practice of hand hygiene, respiratory hygiene and cough etiquette, wearing well-fitted face masks, and avoiding crowded places will supplement for the same.

Various therapeutic strategies have been used to treat this viral infection, but there have been unsuccessful reports recorded so far. However, natural products including plant-derived compounds and drugs can be a potential therapeutic approach to combat its growth and spreading capacity in the future. In this review, we have discussed the various pathological aspects including synthesis, maturation, infectivity, and diagnostic prospects of COVID-19. Additionally, we have also highlighted the recently used drugs and vaccines in combating SARS-CoV-2 infection.

2. Classification, Origin, Primary Reservoirs, and Hosts of Coronavirus

Adetailed outline of the source and transmission is important for developing preventive strategies for containing the spread of the infection. SARS-CoV-2 belongs to the order Nidovirales and family Cornaviridae. The family comprises two subfamilies, i.e., Torovirinae and Coronavirae. Subsequently, the members of the sub-family Coronaviridae are further divided into four genera: (i) alpha coronavirus, 229E, and NL63 are the human coronaviruses that are responsible for croup and the common cold, (ii) In comparison, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-HKU1, and SARS-CoV are classified as beta coronaviruses, (iii) Gamma coronavirus includes viruses of whales and birds, and (iv) Delta coronavirus comprises viruses isolated from birds and pigs [13]. These viruses infect a wide variety of host species, and diversity among these viruses leads to different pathological outcomes. The coronaviruses with pathological manifestations have been enumerated in Table 1 for a better understanding of the same.

Table 1. List of important pathogenic coronaviruses their host organisms, genera name, and associated clinical manifestations.

S.No.	Name	Host Organism	Genera Name	Clinical Manifestations
1	Feline infectious peritonitis virus	Cat	Alpha	Vasculitis, fever, serositis, with or without effusions
2	Camel alphacoronavirus isolate camel/Riyadh	Camel	Alpha	Asymptomatic
3	Canine CoV/TU336/F/2008	Dog	Alpha	Diarrhea and mild clinical signs
4	SeACoV-CH/GD-01	Pig	Alpha	Acute and severe diarrhea and vomiting
5	TGEV/PUR46-MAD	Pig	Alpha	Diarrhea
6	PRCV/ISU-1	Pig	Alpha	Mild respiratory tract infections (RTIs)
7	PEDV/ZJU-G1-2013	Pig	Alpha	Severe watery diarrhea
8	Human CoV-NL63	Human	Alpha	Mild RTIs
9	Human CoV-229E	Human	Alpha	Mild RTIs
10	MHV-A59	Mouse	Beta	Severe lung injuries and acute pneumonia
11	Equine CoV/Obihiro12-1	Horse	Beta	Leucopenia, fever, and anorexia
12	Bovine CoV/ENT	Cow	Beta	Diarrhea
13	MERS-CoV	Human	Beta	Severe acute respiratory syndrome
14	SARS-CoV	Human	Beta	Severe acute respiratory syndrome
15	Human CoV-OC43	Human	Beta	Mild RTIs
16	Human CoV-HKU1	Human	Beta	Pneumonia
17	IBV	Chicken	Gamma	Severe respiratory disease
18	Beluga Whale CoV/SW1	Whale	Gamma	Terminal acute liver failure and pulmonary disease
19	Sparrow coronavirus HKU17	Sparrow	Delta	Respiratory disease
20	Bulbul coronavirus HKU11	Bulbul	Delta	Respiratory disease

SARS-CoV-2 belongs to the beta coronavirus family as that of extremely pathogenic viruses such as SARS-CoV and MERS-CoV. It is a positive-sense single-stranded RNA (+ssRNA) and an enveloped virus. SARS-CoV-2 is regarded as a novel beta coronavirus infecting humans [14]. Indications have been received from the phylogenetic analysis of the SARS-CoV-2 genome suggesting its close relation (with 88% identity) to two coronaviruses that were bat-derived, SARS-like, and were collected in eastern China in 2018 (bat-SL-

CoVZC45 and bat-SL-CoVZXC21). However, it is genetically different from SARS-CoV (approximately 79% similarity) and MERS-CoV [14]. A further study conducted using the genome sequences of SARS-CoV, RaTG13, and SARS-CoV-2 revealed that there is a better correlation between the virus and a bat coronavirus, BatCoV RaTG13, that had been previously detected in Yunnan province in *Rhinolophus affinis*, which resembles 96.2% of the overall identity of the genome sequence [15]. No evidence of recombination events was found during a study in the genome of SARS-CoV-2 from other viruses that originated from bats such as SARSr-CoVs, SARS-CoVs, and BatCoV RaTG13 [15]. When put together, these findings indicate the original host of the virus could be bats [14,15]. Albeit, there is a need to undertake relevant epidemiological studies to determine whether the transmission of the virus to humans is being facilitated by an intermediate host. It is unlikely that bats are the transmitting agents of the virus to humans due to various reasons [14]. (i) There are suggestions that despite having a relatively long branch sequence identity below 90% with bat-SL-CoVZXC21 and bat-SL-CoVZC45, they are not considered as the direct ancestors of SARS-CoV-2, (ii) In the Hunan Seafood Market, no bats were found being sold or purchased, but there were several non-aquatic animals (including mammals) that were up for purchase, (iii) Other animals have acted as intermediate hosts (camels and civets) in other coronaviruses where the natural reservoir is the bat. The instances include MERS-CoV and SARS-CoV. Though, it is pertinent to mention here that bats do not always require an intermediary host for transmitting the viruses to humans. For instance, in Bangladesh, the Nipah virus was transmitted to humans through bats shedding into the sap of raw date palm [16].

Moreover, the initial focus of the researchers was on palm civets and raccoon dogs as the key reservoirs of the SARS-CoV infection. The research study reported positive results for the viral RNA detection from the samples isolated from civets only in the food market, suggesting civet palms as the secondary hosts [17]. In the year 2001, the samples isolated from healthy individuals were subjected to molecular assessment, and it showed the frequency rate of antibodies against the SARS coronavirus to be 2.5%. This suggests that the circulation of the SARScoronavirus in humans might have started before the outbreak in 2003 [18]. Later on, the suggestion that bats can be a source of viral replication was suggested when it was found that *Rhinolophus* bats have anti-SARS-CoV antibodies [19]. The first emergence of MERS was in Saudi Arabia in 2012 [20]. The zoonotic source for MERS coronavirus was reported to be camels, and the identified etiological agent also belonged to betacoronavirus. During a study conducted recently, MERS coronavirus was also detected in *Pipistrellus* and *Perimyotis* bats, thereby proffering the bats to be the major transmitting medium and key host for the virus [21–23]. It was initially suggested by a group of researchers that snakes can be the possible hosts for the virus, but when the genomic similarity between SARS-like bat viruses and novel coronavirus was established, the statement that only bats can be the key reservoirs received support [24,25]. It was revealed from a detailed analysis of the homologous recombination that the development of the receptor binding spike glycoprotein of novel coronavirus occurs from a yet unknown Beta-CoV and a SARS-CoV (CoVZC45 or CoVZXC21) [26]. Further, more work is required for the eradication of the virus regarding the intermediate zoonotic source's identification that led to the transmission of the virus to humans. However, as predicted by Fan et al., there is also a possibility of another outbreak in a couple of years [27]. This was already expected for the current outbreak caused by SARS-CoV-2 (COVID-19), and it will also be contained as soon as earlier outbreaks. However, the key challenge is to plan and prepare ourselves to combat another zoonotic COVID-19 epidemic more effectively in the future.
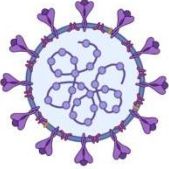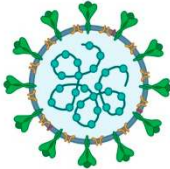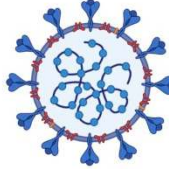
3. Transmission Modes of Coronavirus

Most of the initial cases of COVID-19 had been linked with the Hunan Seafood Market, thereby suggesting that the SARS-CoV-2 have been transmitted to humans from animals. The first mode of disease transmission and the plausible origination of SARS-CoV-2 are not yet wellknown [28]. Initial cluster analysis of infections states that there was a common

point of exposure for infected individuals: a seafood market in Wuhan, Hubei Province, China. The restaurants associated with this market are famous for providing diverse kinds of wild animals for consumption [29]. The role played by the Hunan Seafood Wholesale Market in spreading the disease is not clear yet. However, the Huanan South China Seafood market also trades in live animals, including bats, poultry, marmots, bats, and snakes [25]. This might be a point of zoonotic transmission [29]. Albeit, SARS-CoV-2 is alleged to have zoonotic origination with further human-to-human transmission, but the likelihood of its fecal–oral transmission mandates to rule out the same with additional epidemiological investigations [30]. Though evidence has been provided through a genomic study that the introduction of the virus into the Hunan Seafood Market took place from a yet unknown location, and from there on, it started spreading extremely quickly, but the human-to-human transmission might have started earlier [31]. In addition, it might transmit through direct contact as in other respiratory viruses, such as by shaking contaminated hands or exposure to contaminated surfaces (fomite transmission). Still, other potential routes of SARS-CoV-2 transmission such as blood transfusion, organ transplantation [32], and trans-placental and perinatal transmission need to be adduced more concretely.

The clusters of infected medical personnel and family members have confirmed the occurrence of person-to-person transmission [26]. The aforementioned transmission seemingly occurs among close contacts majorly through respiratory droplets produced upon coughing or sneezing by an infected person. The findings regarding the persistence of SARS-CoV-2 on surfaces for up to 96 h and other coronaviruses for up to 9 days account for a larger aspect of fomite transmission of infection [33,34]. However, the asymptomatic transmission of the infection remains controversial. An initial study that was published on 30 January 2020 reported on asymptomatic transmission, but it has been subsequently found that the researchers failed to direct interview the patient who certainly showed symptoms before disease transmission [35,36]. Another recent study, published on 21 February, also mentioned asymptomatic transmission; however, such studies can be limited due to errors in self-reported symptoms or unknowingly coming in contact with other fomites and cases [37]. The findings regarding the characteristics of the disease have been changing rapidly, and it is important to note that all are subjected to a selection bias. The average incubation period has been pegged at 5.2 days with a 95% confidence interval (95% CI) of 4.1–7.0 days, while the other case studies have reported around 19 or 24 days respectively [38–40]. However, the definition of the case largely relies on a window of 14 days [41]. Estimation of the basic reproductive number (R_0) has been done with varying interpretations and results. The average number of infections that can spread from a single infected individual in a fully susceptible population is measured by R_0 [42]. R_0 was found to be 2.7 for SARS from studies conducted on prior outbreaks and 2.4 for pandemic H1N1 influenza in 2009 [43,44]. Another study estimated the R_0, was 2.2 (95% CI: 1.4–3.9) [40]. However, on further analysis of other 12 available studies, the R_0 was found out to be 3.28 [45]. Though it must be taken into consideration that R_0 only represents an average value, the role of super-spreaders cannot be neglected, as they can be significantly responsible for an outbreak within large clusters, and they would otherwise not affect the value of R_0 significantly [46]. Moreover, R_0 might be unstable during the acute phase of the pandemic [42]. Notably, the comparison between epidemiological profiles of viral infections is enumerated in Figure 1. A study conducted on nine pregnant women who had developed COVID-19 during the later stages of their pregnancy suggested that the development of symptoms in pregnant persons is not any worse than that in non-pregnant persons, and there is no corroborating evidence for vertical transmission causing intrauterine infection [47]. A hospital-based study comprising 138 COVID-19 patients suggested that 41% of patients had a hospital-associated transmission of SARS-CoV-2 infection. Another study suggested a gradual increase in the percentage of cases among health care workers with due course of time [40]. The exposure to a higher concentration of virus due to prolonged contact in proximity is reflected from these case studies.

Disease	MERS	SARS	COVID-19
Disease Causing Viruses	MERS-CoV	SARS-CoV	SARS-CoV-2
Basic Reproductive Number (R_0)	0.3 - 0.8	3	2.0 - 2.5 *
Case Fatality Rate (CFR)	34.4%	9.6 - 11%	~3.4% *
Incubation Duration	6 days	2 - 7 days	4 - 14 days *
Hospitalization Rate	Most cases	Most cases	~19% *
Community Attack Rate	4 - 13%	10 - 60%	30 - 40% *
Annual Infected (global)	420	8098 (in 2003)	N/A (ongoing)

Figure 1. Epidemiological comparison of respiratory viral infections. (*) denotes the data obtained to date. The given percentage values are not fixed as they might change with time.

4. Genome Structure and Life Cycle

The incorporation of three major structural proteins defines the complex structure of the virus. The three proteins accounting for its structure are nucleocapsid protein N that is internally phosphorylated; glycoprotein S, representing the spike; and glycoprotein M, which is an unusual transmembrane protein [48]. The bulky spike, which is found in the viral envelope with peplomers ranging between 15 nm to 20 nm and is represented by the glycoprotein S of 200K [49]. Moreover, the minor transmembrane protein E is also present in the structural region. An envelope protein that performs both the functions of hemagglutination and esterase (HE) is found in several species of coronaviruses [50]. Possessing a genome size of 30 kb, these are single-stranded RNA viruses with a positive-sense RNA [51]. While the 5' end is capped, the 3' terminus is reportedly infectious and is polyadenylated. The expression of individual genes takes place through a complicated process, due to its bigger size, where at the 5' end sequence, the release of the sets of nested mRNAs occurs. Extensive rearrangements facilitate the recombination of heterologous RNA. The leader RNA, which contains 65 to 98 nucleotides in an untranslated (UTR) sequence, occupies the 5' end of the genome along with the 5' end of the remaining sub-genomic mRNAs. At the 3' end of the genome, the poly-A tail incorporates and follows another UTR region comprising 200 to 500 nucleotides. These two UTR regions are accountable for regulating the RNA transcription and replication processes. The genome of the coronavirus contains 7 to 14 open reading frames (ORFs). The beginning portion of the genome has gene one, which is 20–22 kb in length, and spreads across two-thirds of the genome. There are two ORFs, i.e., 1a and 1b, present in this portion, and these ORFs overlap and collectively function as the viral RNA polymerase (Pol). In the genome in this series, four significant structural proteins are incorporated, i.e., 5'–S (spike)–E (envelope)–M (membrane)–N (nucleocapsid)–3' (Figure 2) [52]. The structural proteins are the key player in the virion's assembly and defining the viral infectivity. The homotrimers of S proteins constitute the spikes on the viral surface and facilitate attachment to the host receptors [53,54]. There are three transmembrane domains in the M protein that play

a key role in shaping the virions, promoting membrane curvature, and binding to the nucleocapsid [55,56]. The E protein takes part in the process of assembly and release of the virus along with its involvement in the viral pathogenesis [57,58]. The N protein has two domains with the potentiality of binding the virus RNA genomic material through different mechanisms. It has been reported that N protein can bind to nsp3 protein to tether the genome to the replicase-transcriptase complex (RTC) and packaging the encapsidated genome into virions, respectively [59–61]. This N protein has also been found as an antagonist of the interferon (IFN) and the viral encoded repressor of RNA interference to perquisite the process of viral replication [62]. Within these genes, there are various other ORFs coding for other non-structural proteins such as HE glycoprotein. Depending on the features of the gene order, method of expression, and nucleotide sequence, the marking of each gene in coronavirus is distinct, though all of them are conserved amongst the same serogroup. As other coronaviruses encode smaller ORFs in these regions, the SARS-CoV-2 differs from them in the 3' region of the genome regarding the expression of 8 novel proteins that have been marked as accessory proteins, and these ORFs are presently investigated. Both the ORFs, i.e., 1a and 1b, are identically translated into two poly-proteins at the N-terminus while there is no production of the C-terminal identical polyproteins due to frame-shifting. ORF-1b encodes for a multifunctional helicase protein and the viral RNA-dependent RNA polymerase (RdRp). This protein holds the 5' triphosphatase, NTPase, and dNTPase activities. While all the structural proteins are not essentially required for the process of viral replication, inactivation of the viral function results from the deletion of one or more structural proteins. ORF-3a has a structural protein as one of its products has a role in the viral biogenesis as it is O-glycosylated, possessing the capability to bind S, N, M glycoproteins together, and is triple-membrane spanning in nature [63].

Coronaviruses encode for Mpro (main protease), also known as 3CLpro, which is a chymotrypsin-like protease and has similarities with the 3C protease of picornaviruses [64]. Sixteen non-structural proteins (nsps) are produced due to the remaining polyprotein being further processed by this protease. Among the nsp 1–16, most of the nsps have been found to have a role in the replication of these viruses. However, the functionality of some nsps is yet to be understood. The known functions of the 16 nsps have been summarized in Table 2. SARS-CoV species of coronavirus have the maximum presence of nsps. Nsp3 is one such nsp that has multiplefunctions and contains both protease and ADP-ribose 1″ phosphatase activity [65]. The two proteins nsp7 and nsp8 formulate a cylindrical structure and play a crucial role in synthesizing RNA for coronavirus and single-strand RNA binding protein (nsp9), respectively [66].

The life cycle of these viruses is a multistep event. This includes five steps in the lifecycle of the virus within the host, i.e., attachment, penetration, biosynthesis, maturation, and release [59]. First, the viral S protein attaches to the Angiotensin-Converting Enzyme-2 (ACE2) receptor of the host, then it enters the host cells through membrane fusion or endocytosis. Following the entry, there is aproteolytic cleavage of the virus envelope resulting in the release of genomic RNA in the cytoplasm, and smaller RNAs (sub-genomic mRNAs) are made. The viral RNA enters intothe nucleus for replication once the viral contents enter the host cells. The viral mRNA is used in the biosynthesis procedure for producing viral proteins. The mRNAs further undergo translation procedures to produce several proteins (S, M, N, etc.), which are essentially required for viral assembly. The S, E, and M proteins enter the ER and result in the formation of nucleoprotein complex by combining N protein and genomic RNA (+strand). It is the ER-Golgi apparatus compartment wherein the complete virus particle (proteins and genomic RNA assembly) is formed. Thereafter, the latest viral particles are made and set off through the formation of vesicles and exocytosis, i.e., maturation (Figure 2).

Table 2. Non-structural proteins (nsps) and associated functions.

S.No.	Name	Associated Functions	References
1	nsp1	Inhibits IFNsignaling and involves in cellular mRNA degradation	[67,68]
2	nsp2	Unclear	[69,70]
3	nsp3	Promotescytokine expression, PLP, polypeptides cleaving and blocks hostinnate immune response	[71,72]
4	nsp4	Involves in double-membrane vesicle (DMV) formation	[73,74]
5	nsp5	Inhibits IFNsignaling, acts as a chymotrypsin-like protease (3CLpro), main protease (Mpro), and cleaves polypeptides	[75–77]
6	nsp6	Restricts DMV formation and autophagosome expansion	[78,79]
7	nsp7	Acts as a cofactor with nsp8 and nsp12	[64,80]
8	nsp8	Primase activity and also acts as a cofactor with nsp7 and nsp12	[66,80,81]
9	nsp9	Involves in dimerization and RNA binding	[82,83]
10	nsp10	acts as a scaffold protein for nsp14 and nsp16	[84–87]
11	nsp11	Unclear	[88]
12	nsp12	Primer dependent RdRp	[66,89,90]
13	nsp13	$5'$ triphosphatase and RNA helicase	[91–93]
14	nsp14	N7-Mtase and exoribonuclease	[94–97]
15	nsp15	Acts as an endoribonuclease and evasion of double-stranded RNA viruses (dsRNA) sensors	[98–100]
16	nsp16	$2'$-O-Mtase avoids MDA5 recognition and negatively regulates innate immunity	[85,86,101]

Specific genes are present in all the coronaviruses in ORF1 downstream regions, which encode the proteins for nucleocapsid, viral replication, and spikes formation [102]. On the outer surface of the coronaviruses, there are glycoprotein spikes that facilitate the entry and attachment of the virus to the host cells. The virus can infect multiple hosts due to loose attachment of the receptor-binding domain (RBD) among the virus [103,104]. Other coronaviruses recognize carbohydrates or aminopeptidases as the key receptor for entry into human cells, while SARS-CoV and MERS-CoV recognize exopeptidases [105]. Cellular proteases determine the entry mechanism of a coronavirus which includes cathepsins and transmembrane protease serine 2 (TMPRSS2) and human airway trypsin-like protease (HAT), that split the spike protein and establish further penetration changes [106,107]. As a key receptor, MERS coronavirus employs dipeptidyl peptidase 4 (DPP4), whileACE2 is required as a key receptor by SARScoronavirus and HCoV-NL63 [101,103]. A typical coronavirus structure with spike protein is possessed by SARS-CoV-2, and it expresses nucleoproteins, polyproteins, and membrane proteins such as papain-like protease, helicase, RNA polymerase, glycoprotein, 3-chymotrypsin-like protease, and accessory proteins [15,108]. To maintain the van der Waals forces, the SARS-CoV-2 spike protein comprisesa 3-D structure in the RBD region [109]. The critical lysine 31 residue on the human ACE2 receptor recognizes the 394 glutamine residue present in the SARS-CoV-2 RBD region [110]. The complete mechanism of SARS-CoV-2 pathogenicity, from attachment to replication, has been elaborated in Figures 2 and 3.
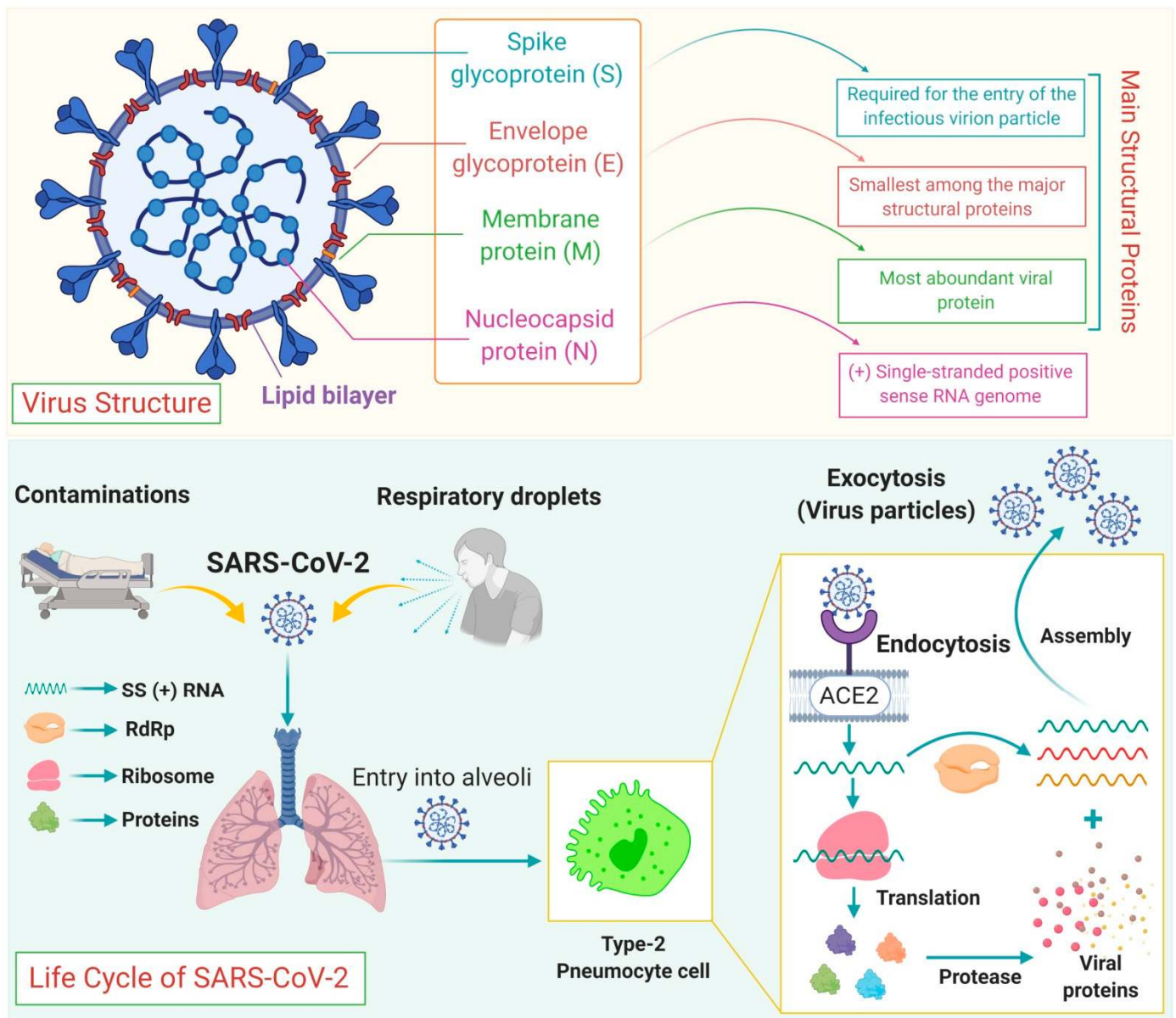
Figure 2. Structure and life cycle of SARS-CoV-2. The life cycle of SARS-CoV-2 is multistep event such as, binding of SARS-CoV-2-ACE2 receptor, proteolytic cleavage and fusion, release of viral RNA and uncoating of nucleoprotein, process of transcription(forming several mRNA transcripts including S, 3a, 3b, E, M, 3, 7a, 7b, 8, and N), replication and packaging of RNA, process of translation, assembly and procedure of budding, exocytosis, and finally, the release of virus takes place.
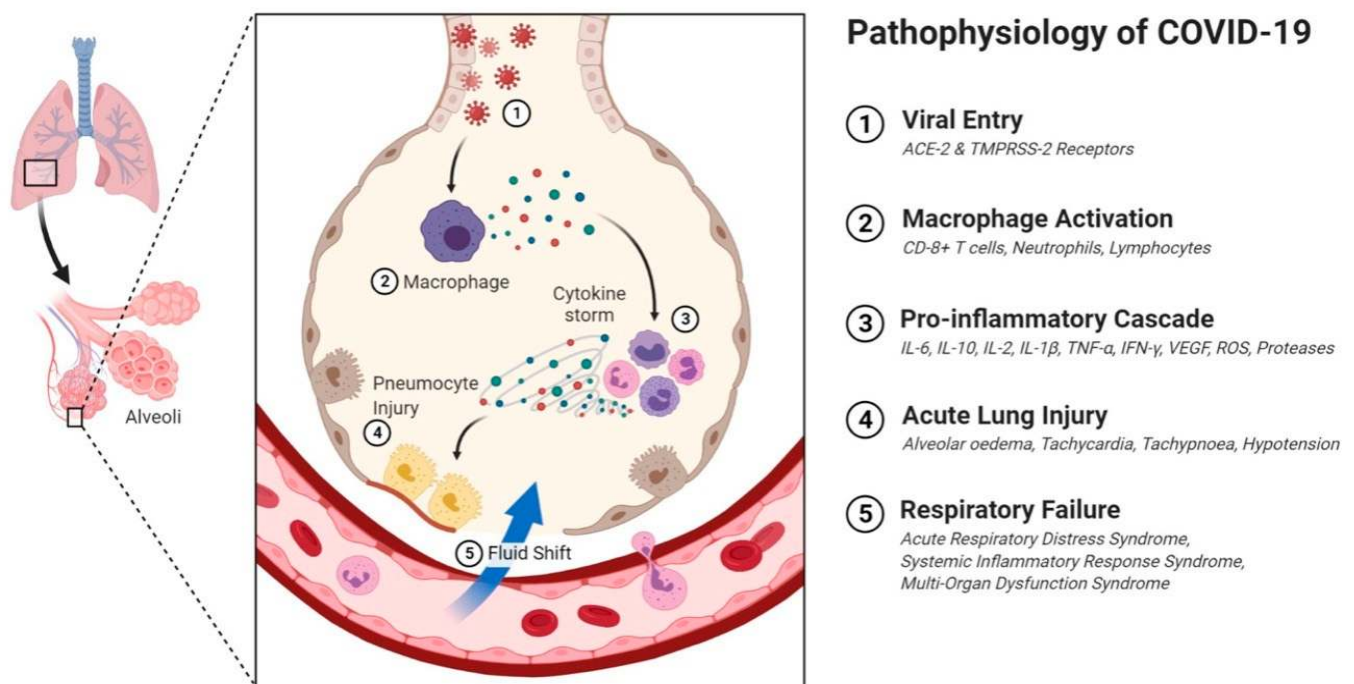
Figure 3. Molecular pathomechanisms of COVID-19.

5. Risk Factors of Coronavirus

Most incidences of SARS-CoV-2 infection are largely observed in adult male patients wherein the patient's median age was between 34 years and 59 years [37,38,111,112]. People suffering from chronic comorbidities like cerebrovascular diseases, cardiovascular ailments, and diabetes are more likely to be infected by the SARS-CoV-2 [113]. In adults 60 years and above, there has been the highest proportion of severe cases along with individuals with existing comorbidities such as cerebrovascular diseases, cardiovascular ailments, and diabetes [37,111]. Co-infections caused by fungi and bacteria may also be associated with severe manifestations [113]. Interestingly, fewer cases of SARS-CoV-2 infection have been reported among children less than 15 years of age [37,38,111,112]. As per a study published on 29th January and conducted in Wuhan on 425 COVID-19 patients, no cases were reported in children under the age of 15 years [40,114]. However, as of March 14th, 2021 according to the American Academy of Pediatrics, the USA alone hosts 3,231,836 pediatric COVID-19 cases, and these cases contribute 13.2% (3,231,836/24,487,634) of all cases. Overall, there are 4294 cases per every 100,000 children in the entire USA population (data retrieved from https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/, accessed on 14 March 2021).

At a glance, most infected patients showed mild symptoms without fever or pneumonia, having a good prognosis [115]. Notably, a study discovered that a child was asymptomatic despite suffering from radiological ground-glass lung opacities [26]. In a nutshell, children can be less likely to get infected, or even if they are infected, they exhibit milder manifestations as compared to adults. It is more likely that the parents or guardians of such children might not seek treatment, which can lead to underestimation of the instances of the disease in this age group.

6. The Clinical Manifestations of COVID-19

Patients infected with SARS-CoV-2 exhibit clinical manifestations ranging from non-specific mild symptoms to severe pneumonia and damage of organ functions. Most common symptoms are cough (59.4–81.8%), dyspnea (3.2–55.0%), fever (77.4–98.6%), fatigue (38.1–69.6%), sputum production (28.2–56.5%), myalgia (11.1–34.8%), and headache

(6.5–33.9%) [109,116]. Other lesser common symptoms include chest pain, hemoptysis, rhinorrhea, nausea, vomiting, sore throat, diarrhea, and conjunctive congestion. Though according to one study, out of the 140 confirmed COVID-19 patients, 39.6% of individuals exhibited gastrointestinal symptoms [117], and 10.1% of patients infected with COVID-19 exhibited gastrointestinal discomfort at its onset [111]. Though many patients developed a fever after hospitalization when they did not have any fever at the onset of the infection [116], and several patients with severe infection did not have a fever at all. Several clinical manifestations such as dry cough, headache, fever, sore throat, and dyspnea are common symptoms caused by all three viruses, i.e., SARS-CoV, MERS-CoV, and SARS-CoV-2. Though, COVID-19 patients exhibit lesser gastrointestinal involvement as compared to patients suffering from MERS and SARS [118]. Patients infected with MERS have a higher occurrence of renal failure, which, even though is characteristic, is not commonly found in other types of coronavirus infections in humans [119,120].

7. Effect of ACE-2 on SARS-CoV-2 Infection

A transmembrane trimetric glycoprotein that protrudes from the viral surface makes up the spike and determines the host tropism and the diversity of the coronaviruses. There are two functional sub-units of a spike where subunit S1 performs the function of binding to host cell receptors, and subunit S2 works for the fusion of cellular and viral membranes. The functional receptor for SARS-CoV has been identified as the ACE2 [121]. It has been shown through structural and functional analysis that ACE2 binds to spike for SARS-CoV-2 [122–124]. The expression for ACE2 was on the higher side in the heart, kidney lung, ileum, and bladder [125]. Inside the lung, lung epithelial cells had a higher expression of ACE2. This is associated with heart function and the development of systemic diseases such as diabetes mellitus, and hypertension. Besides the above, it has been earmarked as the main receptor for coronaviruses, such as SARS-CoV and SARS-CoV-2. SARS-CoV-2 (causing COVID-19 infection) is activated by binding the S glycoprotein to ACE2, which is expressed in the lungs and heart [126]. The virus SARS-CoV-2 has been reported to primarily attack alveolar epithelial cells, which results in severe respiratory symptoms (Figure 4). These symptoms have been reported to have a severe exhibition in cardiovascular disease patients, and this might be linked with increased secretion of ACE2 among these patients compared with healthy individuals. It can be noted that ACE2 levels can be upregulated by using renin-angiotensin–aldosterone system inhibitors [127]. Since ACE2 has been found as the functional receptor for SARS-CoV-2 infection, it is important to be vigilant for the potential effects of antihypertensive treatment using ACE inhibitors or angiotensinreceptor blockers (ARBs) in patients with COVID-19. The switching of the antihypertensive agent from ACE inhibitors/ARBs in COVID-19-infected individuals with hypertension as an underlying disease to other treating agents is seemingly controversial and requires adducing solidly for the same [128].
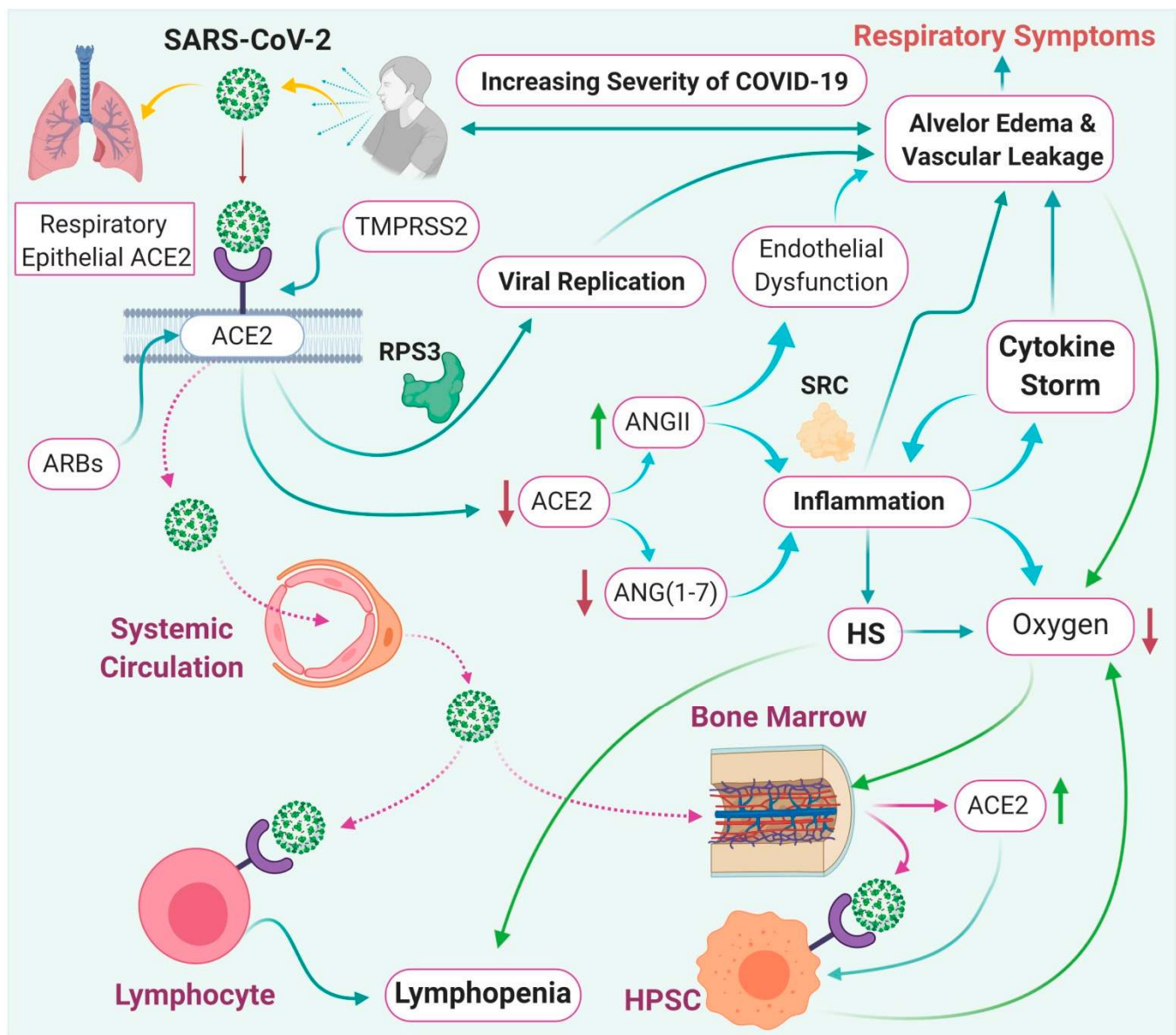
Figure 4. This schematic describes the proposed mechanistic role of ACE2 on SARS-CoV-2 infection. The SARS-CoV-2 virus uses the ACE2 receptor to gain entry into the cell (airway epithelial cells), leading to an increase in proinflammatory cytokines and the development of cytokine storm, which lead to lung damage and augmented COVID-19 severity. Angiotensin receptor blockers (ARBs) might increase the expression of ACE2, and TMPRSS2 assists in S protein priming, leading to enhanced binding of SARS-CoV-2 and higher proinflammatory cytokine release. The higher expression of ACE2 is reported to affect SRC and RPS3, the two crucial genes engaged in inflammatory responses and viral replication. Further, the expression of ACE2, at the same time, is enhanced by the infection. It is also evident that at the same time, SARS-CoV-2 may downregulate ACE2 expression, which further contributes to an increase in angiotensin-2-induced lung injury. The ACE2-mediated negative regulatory activity is curtailed by SARS-CoV-2 and contributes to aggravating the severity of illness.

Recently, it has been found that there was no significant difference in the expression level of the ACE2 in individuals with pre-existing comorbidities when compared to healthy populations. However, long-term smoking has been speculated as a risk factor for SARS-CoV-2 infection following the reporting of the elevated expression of ACE2 among cigarette smokers. The analytical findings of ACE2 in SARS-CoV-2-infected cells suggested the involvement of ACE2 receptors to have a regulatory role in the immune response, cytokine secretion, and replication of virus at post-infectious state, also acting as a binding

receptor to facilitate viral entry. Indeed, these findings may render potential insight into the pathogenesis of COVID-19 in the purview of designing effective therapeutic strategies for battling SARS-CoV-2 infection.

It requires further investigation to determine whether SARS-CoV-2 binds to an additional target. The spike protein undergoes protease cleavage after the host protein binds to SARS-CoV-2. A model was proposed to activate spike protein of SARS-CoV and MERS-CoV comprising a two-step sequential protease cleavage, which, for priming, comprises cleavage at the S1/S2 cleavage site and, for activation, cleavage at the S1 site, which is within the S2 subunit and is a position that is adjacent to a fusion peptide [129–131]. S1 and S2 subunits remain non-covalently bound. The distal S1 subunit contributes to the prefusion state after cleavage at the S1/S2 cleavage site and stabilization of the membrane-anchored S2 subunit [123]. Presumably, the spike for the membrane fusion is activated by the subsequent cleavage at the S′2 site through conformational and irreversible changes. This spike of the coronavirus is unusual amongst the viruses because it can be cleaved and activated through a wide range of varied proteases [132]. The existence of the furin cleavage site at the S1/S2 site, is a characteristic that is unique to SARS-CoV-2. During the biosynthesis, the S1/S2 site of the SARS-CoV-2 is completely subjected to cleavage, which is in drastic contrast to the SARS-CoV spike that has been included in the assembly without cleavage [123]. The cleavage was subjected upon the S1/D2 site through varied proteases such as cathepsin L and TMPRSS2, and the virus is made extremely pathogenic by the ubiquitous expression of furin [131,133].

8. Immunopathological Mechanisms of SARS-CoV-2 Infection

When considered at the whole-genome level, close relations have been found between SARS-CoV-2 and bat-SL-CoVZC45 and bat-SL-CoVZXC21, albeit its receptor binding is identical to that of SARS-CoV [134]. Though, it is pertinent to mention here that species specificity is not solely determined by receptor recognition. After binding to the receptive receptor, the innate immune response is generated to counteract the entry of the SARS-CoV-2 into host cells. The innate immune signaling evasion or inhibition is necessary for infecting its new host and enhancing viral productivity. Though, how SARS-CoV-2 has driven the pathogenesis as well as evade the immune response is still unknown. SARS-CoV-2 seemingly shares an identical pathological mechanistic to that of SARS-CoV, as SARS and COVID-19 exhibit similar clinical features [38]. While responding to the SARS-CoV-2 infections, for inhibiting the replication of the virus, expression of IFN-stimulated genes (ISGs) is stimulated by the type I interferon (IFN) system.

SARS-CoV-2 encodes over eight viral antagonists that evade the ISG effector function and modulate the induction of cytokines and IFN to overcome the antiviral activity [135]. To inhibit the dissemination and replication of the virus, the host immune system responds via cellular antiviral activity and plays a critical role in subjugating inflammation. However, there is a likelihood of pathological implications coming into play due to the lytic effects of the virus on host cells and exacerbated immune response. The studies that include fever, dry cough, breathlessness, hypoxia, and severe pneumonia have identified the symptomatology in COVID-19 diseased patients [38,113]. Some patients witnessed rapid progression combined with Acute Respiratory Distress Syndrome (ARDS), Systemic Inflammatory Response Syndrome (SIRS), and Multi-Organ Dysfunction Syndrome (MODS) that lead to death in approximately 10% of the patients due to the presence of ACE2 receptor in cardiac, renal, and hepatic tissues [113,136](Figure 3). The evolution of diffuse alveolar damage is due to the increased levels of IFN-γ-induced protein 10 (IP10), pro-inflammatory cytokines (IL-1, -2, -6, -8, -10, and -12), interferon-gamma (IFN-γ), monocyte chemoattractant protein-1 (MCP1), and macrophage inflammatory proteins-1A (MIP1A), in patients diagnosed with SARS [137] (Figure 3). A similar picture of immunopathology has been observed in patients infected with SARS-CoV-2. Significantly higher levels of IP10, MCP1, GSCF, and TNF-α have witnessed in patients admitted to the ICU (intensive care unit) as

compared to non-ICU patients, suggesting that the underlying cause of the severity of the disease can be cytokine storm [38].

Against all expectations, an uncommon phenomenon was seen during the acute phase of the viral infection wherein IL-10 and IL-4 anti-inflammatory cytokines were also increased in those patients [38]. One more interesting finding that has been explained before was that older males are more likely to be infected with SARS-CoV-2 as compared to children, with rare cases being reported in that age group [38,113]. With SARS-CoV-2, the same observation was found in primate models where the aged cynomolgus macaque was found to be more likely to be infected by the virus as compared to young adults [138]. The identification of the host genes of SARS-CoV-2 and virulence factors that facilitate virus crossing of species-specific barrier mandates further studies to recognize the cause of the lethal disease in humans.

9. Diagnosis of COVID-19

There are several ways to diagnose and test the impact of SARS-CoV-2 infection such as complete hematological profiling with cellular counts; functional assays of the liver and kidney with the estimate of their enzyme markers and urea levels, respectively; detection of the pathogenic DNA from quantitative PCR or the nucleic acid amplification test; inflammatory markers such as CK-MB, ESR, CRP, D-dimer, ferritin, IL-6, and procalcitonin; and radiological investigations such as chest radiographs, ultrasound, and CT. Quantitative real-time PCR is the mainstay in diagnosing COVID-19 due to its sensitivity, specificity, and feasibility as compared to viral culture. It is the gold standard diagnostic approach with high sensitivity to the viral detection. Elevated procalcitonin levels may also show a superinfection of SARS-CoV-2, as the viral infection may cause a superinfection with bacteria. Similarly, increased levels of biological markers such as IL-6, CRP, ferritin, LDH, D-dimer, and ESR may signify the critical stage of SARS-CoV-2 infection. Further, estimating the complete blood picture report including the count of RBC, WBC, and platelets is another approach to examine SARS-CoV-2 infection. Common laboratory abnormalities present amongst the patients suffering from COVID-19 include prolonged prothrombin time, lymphopenia, and elevated lactate dehydrogenase [37,111,113]. Compared to non-ICU patients, patients admitted to ICU exhibited higher laboratory abnormalities [38,111]. Some patients exhibited elevation in levels of creatine kinase, aminotransferase, creatinine, and C-reactive protein [26,37,38]. Normal serum procalcitonin levels were seen in most of the patients [37,38,111]. High levels of IFN-γ, IP10, IL1β, and MCP1 are present in COVID-19 patients. Importantly, ICU-admitted patients tend to have higher levels of MCP1A, MIP1A, granulocyte-colony stimulating factor (GCSF), IP10, and TNF-α [38]. Further, there can be variations of radiology findings in patients according to immunity status, disease progression, comorbidity, age, and initial medical intervention [139]. In a study conducted amongst the initial 41 cases of 2019-nCoV infection, all 41 patients were suffering from pneumonia, and chest computer tomography (CTscan) showed abnormal findings [38]. In another study comprising six patients, patients who showed multifocal patchy opacities with ground-glass appearances in the peripheral sections of the lungs also exhibited abnormalities on the chest CTscan [26]. As per the data derived from studies, consolidative pulmonary opacities and bilateral pulmonary parenchymal ground-glass are the typical findings of chest CTscans [37,38,111–113,140]. Lung consolidation was noted predominantly among patients five or more days from the onset of disease and those who were 50 years or older compared to those at four or fewer days from onset and those who were 50 years or younger [141]. Manifested by extension and increasing density of the lung opacities, the progression of the disease was noted to be mild to moderate as the course of the disease continued [142]. Sub-segmental and bilateral multiple lobular areas of consolidation are the common findings on chest CTscan in ICU-admitted patients [38]. In a study conducted amongst 99 patients, imaging examination revealed pneumothorax in one patient [113]. The overall diagnosis methods are presented in Figure 5.
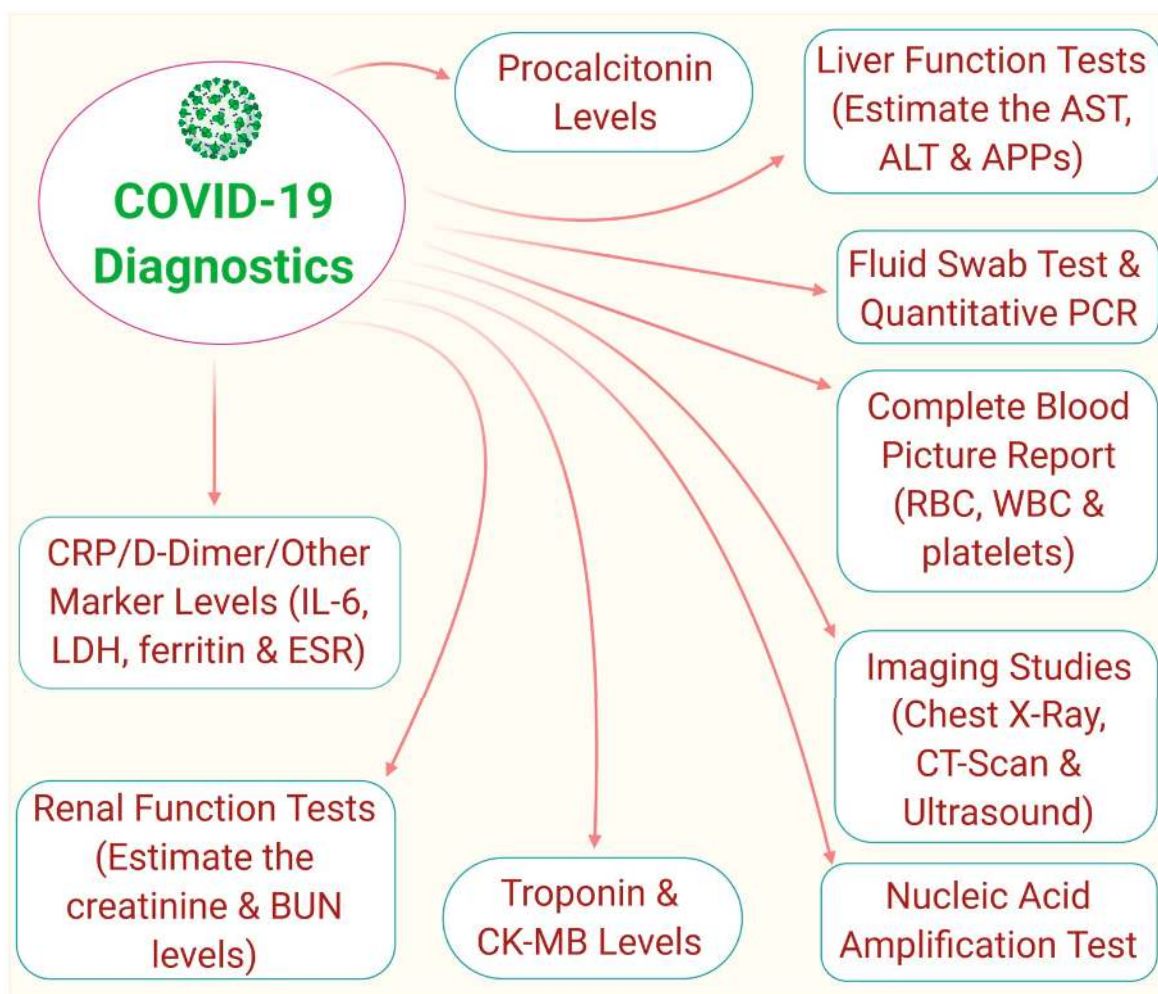
Figure 5. Schematic depiction showing various diagnosis and testing ways of COVID-19.

10. Therapeutic Strategies

Unfortunately, to date, no single medication has been reported or proposed to combat the infective viral load of SARS-CoV-2. However, previous strategies for developing proper medications to pulverize SARS-CoV can be extrapolated to COVID-19 infection effectively. Scientists, several research groups, and clinicians across the globe are working towards finding effective medications that can curtail or eliminate the viral load of SARS-CoV-2. Yet, a definitive treatment to fight COVID-19 needs to be announced across the nations. Further, identifying and implementing various natural products, antiviral drugs, anti-malarial drugs, and vaccines can aid in the treatment of the ongoing pandemic (Figure 6). Social distancing, hand washing, self-isolation, fluid management, oxygen therapy (supportive care), and antibiotics treatment for secondary bacterial infections have been recommended [143]. The deployment of primary prevention of risk factors (social distancing, hand washing, face masks, and other infection control measures) hasbeen addressed and propagated to contain the novel coronaviral agent among communities [144]. Since proper evidence-based treatment was not available for COVID-19, the WHO has framed the guidelines to manage the disease based on triage. Once sepsis in COVID-19 patients is suspected, the rational use of multiple antibiotics and glucocorticoids to control the cytokine storm was suggested. The routine use of glucocorticoid administration is not recommended until and unless it is definitively indicated [144]. Corticosteroid treatment is also not prescribed, as evidenced by several clinical studies [145]. A few studies suggested that the administration

of intravenous immunoglobulin might help in combating SARS-CoV-2 infection in severely ill patients [146].
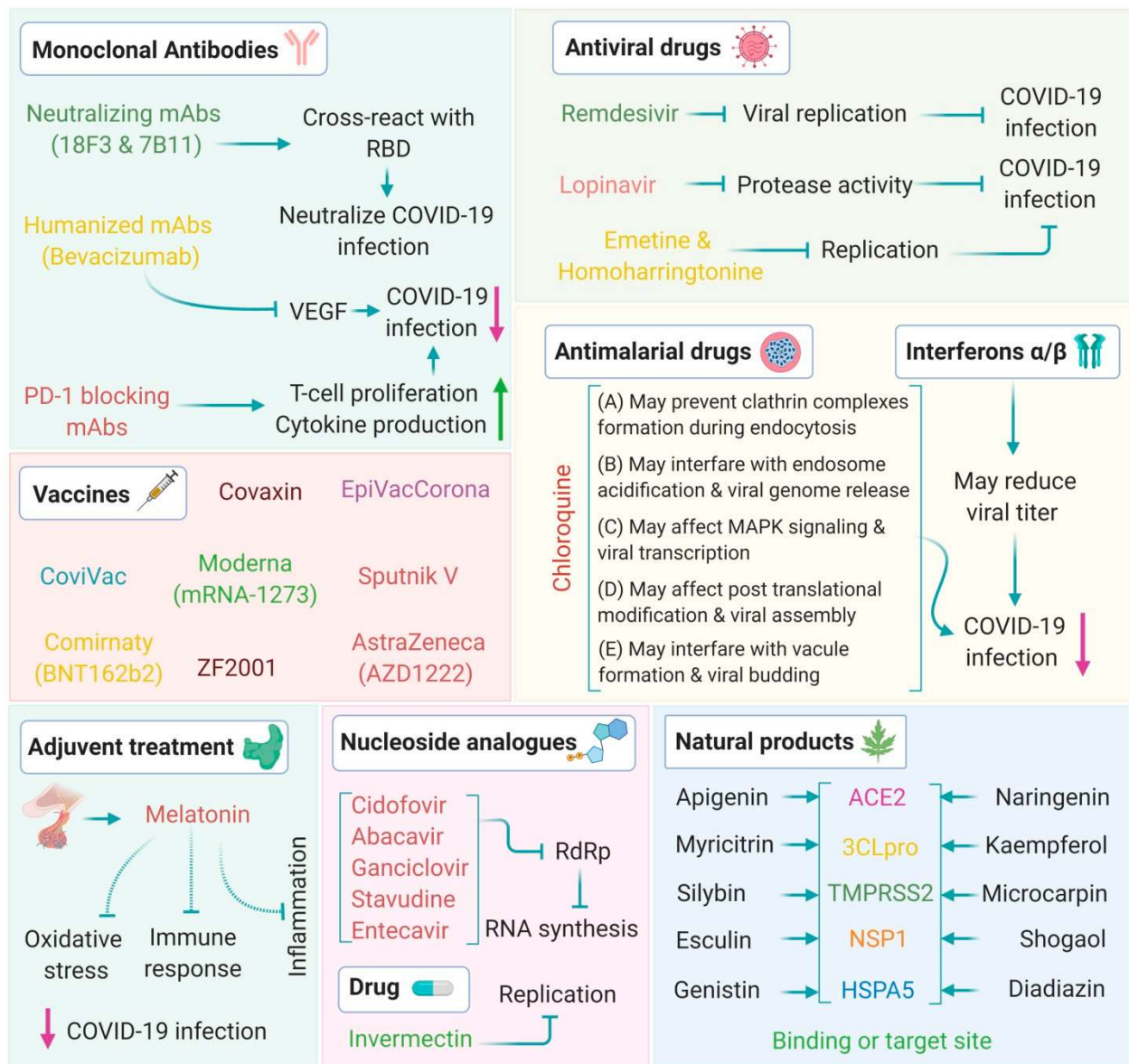
Figure 6. Possible therapeutic strategies to combat SARS-CoV-2 infection.

10.1. Antiviral Drugs

There are no proven studies available to state that anti-viral treatment can combat SARS-CoV-2 infections. Initially, anti-viral drugs, broad-spectrum antibiotics, and effective nebulization of IFN-α had been utilized to curtail this load; though, only a few drugs have displayed their potential impact against the virus [147–149]. Aligning to prior therapeutics investigations for treating MERS and SARS infection, drugs are being evaluated [150]. In general, there is a lack of strong evidence that antiviral drugs can considerably improve the clinical outcomes. Researchers have also used the anti-influenza drug oseltamivir in combination with empirical antibiotics as a cocktail in the management of COVID-19 patients [38]. Similarly, in the US, Remdesivir developed for the Ebola virus has been recently utilized along with other antimicrobials to combat COVID-19 [151]. Certain potential clinical advantages were observed on a few COVID-19 patients when administered with the combination of Arbidol/ShufengJiedu Capsule (SFJDC) and Ritonavir/Lopinavir [111]. To

examine the safety and effectiveness of Lopinavir/Ritonavir and interferon-2b in COVID-19 patients, a clinical study is under trial [143]. A broad-spectrum antiviral drug, Remdesivir, a nucleotide analog RNA polymerase inhibitor, has shown efficacy against SARS-CoV-2 in *in-vitro* and *in-vivo* studies and clinical trials [12,122]. It has been reported that patients suffering from coronaviruses were affirmed as clinically recovered after the administration of Remdesivir. This antiviral drug alone or in combination with chloroquine or IFN-β significantly blocks SARS-CoV-2 replication [151,152]. Intravenous Remdesivir cured the first case of COVID-19 reported from the USA, along with other supportive care [12]. However, the establishment of definitive effects of Remdesivir on SARS-CoV-2 further warrants detailed research work in animals and clinical sample-based settings. A range of other antiviral drugs is presently under evaluation against SARS-CoV-2 infection. *In vitro* studies on Nitazoxanide, Nafamostat, Penciclovir, Ribavirin, Arbidol, Favipiravir, Ritonavir, Baricitinib, and AAK1 showed moderate results against COVID-19 [111,151–153]. Similarly, several other combinations, including combining traditional Chinese medicines with antiviral or antibiotics, have been evaluated in humans and mice against SARS-CoV-2-induced infection [152]. Additionally, the drugs from existing antiviral categories hold scope for future prospects [154,155] (Table 3).

Table 3. List of natural products/isolated compounds or their derivatives and drugs that inhibit the coronavirus family.

Categories	Compound Name	Proposed Mode of Actions	Involved Viruses	References
Antiviral drugs	Remdesivir (GS-5734, Nucleoside analogue of Remdesivir triphosphate) (RDV-TP)	Inhibitor of RdRp	SARS-CoV-2	[156]
	Lopinavir/Ritonavir	HIV protease inhibitor	HIV infection, SARS-CoV-1, and MERS-CoV	[157,158]
	Darunavir/Cobicistat	Protease inhibitor	SARS-CoV-2	[159]
	Favipiravir (T-705) Purine nucleotide	RNA polymerase inhibitor	RNA viruses and SARS-CoV-2	[160]
	Ribavirin (Guanine analogue)	Inhibits viral RdRp	SARS-CoV-1 and SARS-CoV-2	[161]
	Umifenovir (Arbidol)	Targeting the S protein/ACE2 and inhibits the membrane fusion of the envelope of the virus	Influenza and SARS-CoV-2	[162,163]
Antimalarial drugs	Chloroquine (Synthetic version of quinine and is found in the bark of cinchona trees)	Reduces the rate of replication	Malaria, systemic inflammatory diseases, and SARS-CoV-2	[164]
	Hydroxychloroquine	Inhibition of glycosylation of host receptors, proteolytic processing, and acidification of endosomes	SARS-CoV-2 and autoimmune diseases	[165]
Antiparasitic drugs	Ivermectin	Inhibits nuclear transport	Parasitic Infections and SARS-CoV-2	[166]
	Nitazoxanide (Anti-helminthic drug)	Unclear	MERS and SARS-CoV-2	[167]

Table 3. *Cont.*

Categories	Compound Name	Proposed Mode of Actions	Involved Viruses	References
Adjunctive drugs	Corticosteroids/quinolone (n combination)	Prevents ARDS	SARS-CoV and SARS-CoV-2	[168]
	Monoclonal Antibodies (Tocilizumab, Sarilumab, Eculizumab, Fingolimod, Bevacizumab)	Immunomodulatory effect, inhibition of terminal complement, and anti–VEGF medication	SARS-CoV-2 and Chronic Inflammatory disorders	[169,170]
	ACE-Inhibitors and ARBs (enzyme)	Activates RAAS mechanism	SARS-CoV-2	[171]
	Interferon-(α and β)	Unclear	MERS-CoV and SARS-CoV-2	[161]
	Vitamin-D (Adjunct with vitamin C and zinc)	Inhibits inflammatory response and attenuates cytokine storm	SARS-CoV-2	[172,173]

10.2. Vaccines

Usually, vaccine preparation is a three-phase (I, II, III) trial-based procedure. The conduction of phase I trial aims at checking the generation of immune response by enrolling only multiples of 10 (approximately 30–40) individuals. A successful phase I trial proceeds further to phase II with the further enrollment of hundreds of individuals, wherein the aim is to identify the dosage concentrations, immunogenicity, and safety. Finally, the phase III trial will include the enrollment of thousands of individuals for measuring the efficacy of the vaccine in terms of its immune response against the targeted disease infection. Currently, multiple companies/universities are investigating the development of a vaccination against SARS-CoV-2 with the Coalition for Epidemic Preparedness Innovations [174]. Here we have collated the information on various vaccines that are approved (Table 4) and underdevelopment (Table 5) along with their respective details.

Table 4. List of approved vaccines for COVID-19; data retrieved from https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker, accessed on 14 March 2021.

S.No	Name	Vaccine Type	Primary Developer	Country of Origin	List of Countries Approved for Use
1	Comirnaty (BNT162b2)	mRNA-based vaccine	Pfizer, BioNTech; Fosun Pharma	Multinational	Albania, Andorra, Argentina, Aruba, Australia, Bahrain, Brazil, Canada, Caribbean, Chile, Colombia, Costa Rica, Ecuador, EU, Faroe Islands, Greenland, Hong Kong, Iceland, Iraq, Israel, Japan, Jordan, Kuwait, Liechtenstein, Malaysia, Mexico, Monaco, New Zealand, North Macedonia, Norway, Oman, Panama, Philippines, Qatar, Rwanda, Saint Vincent and the Grenadines, Saudi Arabia, Serbia, Singapore, South Korea, Suriname, Switzerland, UAE, UK, US, Vatican City, WHO

Table 4. *Cont*.

S.No	Name	Vaccine Type	Primary Developer	Country of Origin	List of Countries Approved for Use
2	Moderna COVID-19 Vaccine (mRNA-1273)	mRNA-based vaccine	Moderna, BARDA, NIAID	US	Canada, EU, Faroe Islands, Greenland, Iceland, Israel, Liechtenstein, Norway, Qatar, Saint Vincent and the Grenadines, Singapore, Switzerland, United Kingdom, United States, Vietnam
3	COVID-19 Vaccine AstraZeneca (AZD1222); also known as Covishield	Adenovirus vaccine	BARDA, OWS	UK	Argentina, Bahrain, Bangladesh, Barbados, Brazil, Canada, Chile, Dominican Republic, Ecuador, El Salvador, Egypt, EU, Ghana, Guyana, Hungary, India, Indonesia, Iraq, Ivory Coast, Malaysia, Maldives, Mauritius, Mexico, Morocco, Myanmar, Nepal, Nigeria, Pakistan, Philippines, Saint Vincent and the Grenadines, South Africa, South Korea, Sri Lanka, Taiwan, Thailand, UK, Vietnam
4	Sputnik V	Recombinant adenovirus vaccine (rAd26 and rAd5)	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Russia	Algeria, Angola, Argentina, Armenia, Bahrain, Belarus, Bolivia, Congo, Djibouti, Egypt, Gabon, Ghana, Guatemala, Guinea, Guyana, Honduras, Hungary, Iran, Iraq, Jordan, Kazakhstan, Kenya, Kyrgyzstan, Laos, Lebanon, Mexico, Moldova, Mongolia, Montenegro, Morocco, Myanmar, Nicaragua, North Macedonia, Pakistan, Palestine, Paraguay, Republika Srpska, Russia, Saint Vincent and the Grenadines, San Marino, Serbia, Slovakia, Sri Lanka, Syria, Tunisia, Turkmenistan, United Arab Emirates, Uzbekistan, Venezuela, Zimbabwe
5	COVID-19 Vaccine Janssen (JNJ-78436735; Ad26.COV2.S)	Non-replicating viral vector	Janssen Vaccines (Johnson & Johnson)	The Netherlands, US	Bahrain, Canada, EU, Saint Vincent and the Grenadines, US, WHO
6	CoronaVac	Inactivated vaccine (formalin with alum adjuvant)	Sinovac	China	Azerbaijan, Bolivia, Brazil, Cambodia, China, Chile, Colombia, Ecuador, Hong Kong, Indonesia, Laos, Malaysia, Mexico, Thailand, Tunisia, Turkey, Philippines, Ukraine, Uruguay, Zimbabwe

Table 4. *Cont.*

S.No	Name	Vaccine Type	Primary Developer	Country of Origin	List of Countries Approved for Use
7	BBIBP-CorV	Inactivated vaccine	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	Argentina, Bahrain, Cambodia, China, Egypt, Hungary, Iraq, Jordan, Laos, Macau, Morocco, Nepal, Pakistan, Peru, Senegal, Serbia, Seychelles, UAE, Venezuela, Zimbabwe
8	EpiVacCorona	Peptide vaccine	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	Russia	Russia, Turkmenistan
9	Convidicea (Ad5-nCoV)	Recombinant vaccine (adenovirus type 5 vector)	CanSino Biologics	China	Mexico, China, Pakistan
10	Covaxin	Inactivated vaccine	Bharat Biotech, ICMR	India	India, Zimbabwe
11	No name announced	Inactivated vaccine	Wuhan Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	China
12	CoviVac	Inactivated vaccine	Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products	Russia	Russia
13	ZF2001	Recombinant vaccine	Anhui ZhifeiLongcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences	China, Uzbekistan	Uzbekistan

Table 5. List of vaccine candidates under development along with their clinical trial stages; data retrieved from https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker, accessed on 14 March 2021.

S.No	Candidate Name	Vaccine Type	Sponsor/Developer	Clinical Trial Stage	Companies/Universities
1	NVX-CoV2373	Nanoparticle vaccine	Novavax	Phase 3	Novavax
2	ZyCoV-D	DNA vaccine (plasmid)	Zydus Cadila	Phase 3	Zydus Cadila
3	Abdala (CIGB 66)	Protein subunit vaccine	Center for Genetic Engineering and Biotechnology	Phase 3	Center for Genetic Engineering and Biotechnology
4	CVnCoV	mRNA-based vaccine	CureVac; GSK	Phase 2b/3	CureVac

Table 5. *Cont.*

S.No	Candidate Name	Vaccine Type	Sponsor/Developer	Clinical Trial Stage	Companies/Universities
5	Bacillus Calmette-Guerin (BCG) vaccine	Live-attenuated vaccine	University of Melbourne and Murdoch Children's Research Institute; Radboud University Medical Center; Faustman Lab at Massachusetts General Hospital	Phase 2/3	University of Melbourne and Murdoch Children's Research Institute; Radboud University Medical Center; Faustman Lab at Massachusetts General Hospital
6	INO-4800	DNA vaccine (plasmid)	Inovio Pharmaceuticals	Phase 2/3	Center for Pharmaceutical Research, Kansas City. Mo.; University of Pennsylvania, Philadelphia
7	VIR-7831	Plant-based adjuvant vaccine	Medicago; GSK; Dynavax	Phase 2/3	Medicago
8	No name announced	Adenovirus-based vaccine	ImmunityBio; NantKwest	Phase 2/3	NA
9	UB-612	Multitope peptide-based vaccine	COVAXX	Phase 2/3	United Biomedical Inc. (UBI)
10	No name announced	Recombinant protein vaccine	Sanofi; GlaxoSmithKline	Phase 2	Various
11	BNT162	mRNA-based vaccine	Pfizer, BioNTech	Phase 1/2/3	Multiple study sites in Europe, North America and China
12	Soberana 1 and 2	Monovalent/conjugate vaccine	Finlay Institute of Vaccines	Phase 1/2/3	Finlay Institute of Vaccines
13	AdCLD-CoV19	Adenovirus-based vaccine	Cellid; LG Chem	Phase 1/2a	Korea University Guro Hospital
14	Nanocovax	Recombinant vaccine (Spike protein)	Nanogen Biopharmaceutical	Phase 1/2	Military Medical Academy (Vietnam)
15	EuCorVac-19	nanoparticle vaccine	EuBiologics	Phase 1/2	Eunpyeong St. Mary's Hospital
16	Mambisa (CIGB 669)	Protein subunit vaccine	Center for Genetic Engineering and Biotechnology	Phase 1/2	Center for Genetic Engineering and Biotechnology
17	IIBR-100	Recombinant vesicular stomatitis virus (rVSV) vaccine	Israel Institute for Biological Research	Phase 1/2	Hadassah Medical Center; Sheba Medical Center Hospital
18	No name announced	SF9 cell vaccine candidate	West China Hospital, Sichuan University	Phase 1/2	West China Hospital, Sichuan University
19	VLA2001	Inactivated vaccine	Valneva; National Institute for Health Research (NIHR)	Phase 1/2	Multiple NIHR testing sites
20	No name announced	Adjuvanted protein subunit vaccine	CEPI	Phase 1/2	NA

Table 5. *Cont*.

S.No	Candidate Name	Vaccine Type	Sponsor/Developer	Clinical Trial Stage	Companies/Universities
21	AG0301-COVID19	DNA vaccine	AnGes, Inc.	Phase 1/2	AnGes, Inc.; Japan Agency for Medical Research and Development
22	GX-19N	DNA vaccine	Genexine	Phase 1/2	
23	ARCT-021 (LUNAR-COV19)	Self-replicating RNA vaccine	Arcturus Therapeutics and Duke-NUS Medical School	Phase 1/2	Duke-NUS Medical School, Singapore
24	No name announced	Inactivated vaccine	Chinese Academy of Medical Sciences, Institute of Medical Biology	Phase 1/2	West China Second University Hospital, Yunnan Center for Disease Control and Prevention
25	HDT-301 (HGCO19)	RNA vaccine	University of Washington; National Institutes of Health Rocky Mountain Laboratories; HDT Bio Corp; Gennova Biopharmaceuticals	Phase 1/2	NA
26	AV-COVID-19	Dendritic cell vaccine	Aivita Biomedical, Inc.	Phase 1b/2	Rumah Sakit Umum Pusat DrKariadi
27	PTX-COVID19-B	mRNA-based vaccine	Providence Therapeutics; Canadian government	Phase 1	NA
28	COVI-VAC	Intranasal vaccine	Codagenix; Serum Institute of India	Phase 1	NA
29	CORVax12	DNA vaccine (plasmid)	OncoSec; Providence Cancer Institute	Phase 1	Providence Portland Medical Center
30	MVA-SARS-2-S	Modified vaccinia virus ankara (MVA) vector vaccine candidate	Universitätsklinikum Hamburg-Eppendorf; German Center for Infection Research; Philipps University Marburg Medical Center; Ludwig-Maximilians-University of Munich	Phase 1	University Medical Center Hamburg-Eppendorf
31	COH04S1	Modified vaccinia virus ankara (MVA) vector vaccine candidate	City of Hope Medical Center; National Cancer Institute	Phase 1	City of Hope Medical Center
32	pVAC	Multi-peptide vaccine candidate	University Hospital Tuebingen	Phase 1	University Hospital Tuebingen
33	AdimrSC-2f	Protein subunit vaccine	Adimmune	Phase 1	Adimmune
34	bacTRL-Spike	Monovalent oral vaccine (bifidobacteria)	Symvivo	Phase 1	Symvivo Corporation

Table 5. *Cont*.

S.No	Candidate Name	Vaccine Type	Sponsor/Developer	Clinical Trial Stage	Companies/Universities
35	COVAX-19	Monovalent recombinant protein vaccine	Vaxine Pty Ltd.	Phase 1	Royal Adelaide Hospital
36	DelNS1-2019-nCoV-RBD-OPT1	Replicating viral vector	Xiamen University, Beijing Wantai Biological Pharmacy	Phase 1	Jiangsu Provincial Centre For Disease Control and Prevention
37	GRAd-COV2	Adenovirus-based vaccine	ReiThera; Leukocare; Univercells	Phase 1	Lazzaro Spallanzani National Institute for Infectious Diseases
38	UQ-CSL V451	Protein subunit vaccine	CSL; The University of Queensland	Phase 1	NA
39	SCB-2019	Protein subunit vaccine	GlaxoSmithKline, Sanofi, Clover Biopharmaceuticals, Dynavax and Xiamen Innovax; CEPI	Phase 1	Linear Clinical Research (Australia)
40	VXA-CoV2-1	Recombinant vaccine (adenovirus type 5 vector)	Vaxart	Phase 1	Vaxart
41	AdCOVID	Intranasal vaccine	Altimmune	Phase 1	University of Alabama at Birmingham
42	AAVCOVID	Gene-based vaccine	Massachusetts Eye and Ear; Massachusetts General Hospital; University of Pennsylvania	Pre-clinical	NA
43	ChAd-SARS-CoV-2-S	Adenovirus-based vaccine	Washington University School of Medicine in St. Louis	Pre-clinical	Washington University School of Medicine in St. Louis
44	HaloVax	Self-assembling vaccine	Voltron Therapeutics, Inc.; Hoth Therapeutics, Inc.	Pre-clinical	MGH Vaccine and Immunotherapy Center
45	LineaDNA	DNA vaccine	Takis Biotech	Pre-clinical	Takis Biotech
46	MRT5500	mRNA-based vaccine	Sanofi, Translate Bio	Pre-clinical	NA
47	No name announced	Ii-Key peptide COVID-19 vaccine	Generex Biotechnology	Pre-clinical	Generex
48	No name announced	Protein subunit vaccine	University of Saskatchewan Vaccine and Infectious Disease Organization-International Vaccine Centre	Pre-clinical	University of Saskatchewan Vaccine and Infectious Disease Organization-International Vaccine Centre
49	No name announced	mRNA-based vaccine	Chulalongkorn University's Center of Excellence in Vaccine Research and Development	Pre-clinical	NA

Table 5. *Cont.*

S.No	Candidate Name	Vaccine Type	Sponsor/Developer	Clinical Trial Stage	Companies/Universities
50	No name announced	gp96-based vaccine	Heat Biologics	Pre-clinical	University of Miami Miller School of Medicine
51	No name announced	Inactivated vaccine	Shenzhen Kangtai Biological Products	Pre-clinical	NA
52	PittCoVacc	Recombinant protein subunit vaccine (delivered through microneedle array)	UPMC/University of Pittsburgh School of Medicine	Pre-clinical	University of Pittsburgh
53	T-COVIDTM	Intranasal vaccine	Altimmune	Pre-clinical	NA
54	LNP-nCoVsaRNA	Self-amplifying RNA vaccine	Imperial College London	No longer being studied	Imperial College London
55	V590	Recombinant vaccine (vesicular stomatitis virus)	Merck; IAVI	No longer being studied	NA
56	V591	Measles vector vaccine	University of Pittsburgh's Center for Vaccine Research	No longer being studied	University of Pittsburgh; Themis Biosciences; Institut Pasteur

11. Other Promising Therapeutics

In China, the medical researchers collected plasma from COVID-19 recovered patients and re-infused it into clinically ill patients who showed complete recovery from COVID-19 disease with good pulmonary compliance. Recently, CR3022 (monoclonal antibody) binding with the spike RBD of SARS-CoV-2 has also been identified, and this is probably due to the antibody's epitope not overlapping with the divergent ACE2 receptor-binding motif. With the pieces of the available evidence on CR3022 (monoclonal antibody), it can be plausibly used as a therapeutic to treat COVID-19 [175]. Recently, Remdesivir, lopinavir, emetine, and homoharringtonine have also reported inhibiting SARS-CoV-2 replication *in vitro* [176]. Further, the sensitivity of SARS-CoV-2 to recombinant human interferons α and β (IFNα/β) has also been observed. Treatment with IFN-α or IFN-β at a concentration of 50 international units (IU) per milliliter reduces the viral titers by 3.4 log or over 4 log, respectively, in Vero cells. The noted EC50 of IFN-α and IFN-β treatment is 1.35 IU/mL and 0.76 IU/mL, respectively, in Vero cells. These results suggest the higher sensitivity of SARS-CoV-2 compared to other human pathogenic viruses, including SARS-CoV. Overall, this study shows the potential efficacy of human type-I IFN in suppressing SARS-CoV-2 infection, a finding which could inform future treatment options for COVID-19 [177]. Further, usingneutralizing antibodies against SARS-CoV-2 (anti-SARS-CoVnAbs) can be an alternative approach to prevent SARS-CoV-2 infection [178].

The utilization of nucleotide analogs can be another potential approach to treat COVID-19. These nucleotide analogs have the potential to evade the exonuclease activity of the virus. In this context, it is noteworthy that the prodrugs of five of these nucleotide analogs (Cidofovir, Abacavir, Valganciclovir/Ganciclovir, Stavudine, and Entecavir) are FDA-approved medications for treating other viral infections with well-established safety profiles. To reiterate, following the demonstration of the inhibiting potency of viral replication in cell culture, the candidature molecules are subjected to being evaluated as potential therapies for COVID-19 [179]. Further, type 1 interferons can be more helpful in treating COVID-19. The experience and knowledge inferred from the IFN-I treatment against SARS-CoV and MERS-CoV prove valuable in the selection of potential treatments against SARS-CoV-2 [180].

Interestingly, Ivermectin, a FDA-approved anti-parasitic agent, has previously showed broad-spectrum antiviral activity *in vitro*, as an inhibitor of the causative virus (SARS-CoV-2), with a single addition to Vero-hSLAM cells 2 h post-infection with SARS-CoV-2 able to effect ~5000-fold reduction in viral RNA at 48 h. Therefore, this agent warrants further investigation to perquisite humans [166].

Due to the drastic improvement in the field of molecular biology and translational science, cellular therapy has emerged as a potential option for combating COVID-19 [181]. Cellular therapy deals with the usage of autologous or allogenic pooled conditioned stored cells to treat the disease and to regenerate the damaged cells, tissues, or organs. Researchers have thrown the limelight on the usage of various cells like bone marrow mesenchymal stem cells, adipose tissue-derived mesenchymal stem cells, and placental-derived mesenchymal stem cells (MSCs) to curb COVID-19 pneumonia. A total of 53 clinical trials have been in the recruiting status and are ongoing. The results of these trials are awaited (ClinicalTrials.Gov). Despite the advantage of regenerating the damaged pulmonary epithelium, MSCs have quite a list of challenges when administering to patients with COVID-19. The challenges in the usage of cellular therapy are isolation, harvesting, and characterization of cells, preparation protocols, route of administration, dose, and frequency of treatment, immune privilege nature, and the expected outcome of the cells that have been transfused. Outweighing the challenges, cellular therapy has a ray of hope to curb COVID-19 pneumonia.

The natural metabolites of the different chemical agents present a ray of hope, and promising data on virtual molecular docking hasbeen enumerated in Table 6. Despite the distinct molecular structure, several chemical agents (flavanones, flavonols, alkaloids, fatty acids, quinones, terpenes, and steroids) possess similar docking forces to the repurposed drugs (e.g., Remdesivir and Chloroquine) with proteins/signals/receptors involved in SARS-CoV-2 replication, including ACE2, 3CLpro, and TMPRSS-2. It can be inferred from the docking evaluation that inhibitors of ACE2 retard the binding capacity of SARS-CoV-2 and arrest the viral entry into pulmonary epithelium [182,183]. Considering the blockade of SARS-CoV-2 infection through the ACE2 receptor, the lowest affinity was possessed by Flavolignan silybin. Rahma et al. [184] suggested 12 natural metabolites having binding energy with TPMRSS2 ranging from -11.06 to-14.69 kcal mol. The search for TMPRSS2 inhibitors is lowered within the major replication proteins, despite that molecular docking shows another strategy to be investigated for treating COVID-19 [133]. Notably, the role of TMPRSS2 in inoculation and replication of influenza virus, cancer, and SARS-CoV-1 [185] has been well-documented. Besides, researchers are more promptly searchingfor strategies to target the inhibition of the main protein (3CLpro) of SARS-CoV-2, as it could prevent the inoculation of the virus in the host [186–188]. Although the 3CLpro is an enzyme specific to the virus, the one within SARS-CoV-2 has a large structural similarity with the one present in SARS-CoV-1 (96.08%) [182]. *In silico* analysis demonstrated that the terpenoids Bonducellpin D and Caesalmin B and the flavonoid 5,7-dimethoxy flavanone-40-O-b-d-glucopyranoside have binding affinities with 3CLpro of SARS-CoV-1, SARS-CoV-2, and MERS-CoV ranging from -8 to -11 kcal mol^{-1}, an outstanding value compared to repurposed drugs (Table 6).

Table 6. Recently evaluated natural metabolites against COVID-19 by virtual docking.

Target/Binding Site	Natural Products/Metabolites	Binding Energy (kcal mol^{-1})	Reference
ACE2	Zhebeininoside	−6.8	[189]
	Verdine	−6.6	
	Pseudojervine	−6.8	
	Imperialine-3-b-D-glucoside	−7.1	
	Hupehemonside	−7.1	
	Nobiletin	−5.42	[190]
	Neohesperidin	−3.78	
	Hesperetin	−6.09	
	Hesperidin	−4.21	
	Naringenin	−6.05	
	Narigin	−6.85	
	Chloroquine	−8.019	[191]
	Philligenin	−7.807	
	Hinokinin	−7.11	
	Withaferin A	−9.631	
	Quercetin	−8.664	
	Isoaloresin	−7.835	
	Aloin	−8.383	
	Corydine	−6.041	
	Tetrahydrocurcumin	−8.009	
	Silybin	−10.572	
	Isoquercitrin	−7.8	[192]
	Afzelin	−7.1	
	Oriciacridone F	−6.7	
	Remdesivir	−7.8	
	Cassameridin	−8.1	
	(-)-Asperlicin C	−9.5	
	Kaempferol	−7.2	
	Apigenin	−7.1	
	Myricitrin	−7.1	
	Vitetrifolin D	−7.3	
	Lactucopicrin	−8.3	
	Lactucopicrin 15-oxalate	−8.3	
	Taiwanhomoflavone A	−7.6	
	Epicatechin-(4b,8)-epicatechin-(4b,6)-catechin	−8.2	
	Epicatechin-4-epigallocatechin	−7.2	
	Quercetin 3-glucosyl-(1,4)-rhamnoside	−6.5	

Table 6. *Cont.*

Target/Binding Site	Natural Products/Metabolites	Binding Energy (kcal mol^{-1})	Reference
3CLpro	Epicatechin-gallate	−6.27	[193]
	α-Copaene	−20.08	[194]
	(E)-β-Farnesene	−27.56	[194]
	Gingerol	−5.38	
	Zingerol	−5.4	
	Apigenin-7-glucoside	−7.83	[193]
	Quercetin	−8.47	
	Kaempferol	−8.58	
	Lopinavir	−9.41	
	Nelfinavir	−10.74	
	Sugiol	−6.04	
	N-cis-feruloyltyramine	−6.25	[195]
	Cryptotanshinone	−6.23	
	Betulinic acid	−4.23	
	Amaranthin	−18.14	
	Methyl rosmarinate	−20.62	[196]
	5,7,3',4'-tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone	−29.57	
	Mirycitrin	22.13	
	Zeylanone	−9.12	
	Glabrolide	−9.16	[197]
	Amentoflavone	−9.28	
	Isoquercitrin	−8.2	
	Afzelin	−8.8	
	Oriciacridone F	−9.1	
	Remdesivir	−8.2	
	Cassameridin	−9.3	
	Kaempferol	−7.8	
	(-)-Asperlicin C	−9.7	
	Apigenin	−7.8	
	Myricitrin	−8.9	[192]
	Vitetrifolin D	−7.6	
	Lactucopicrin 15-oxalate	−8.2	
	Lactucopicrin	−7.8	
	Quercetin 3-glucosyl-(1,4)-rhamnoside	−9.9	
	Epicatechin-(4',8)-epigallocatechin	−10	
	Epicatechin-(4b,8)-epicatechin-(4b,6)-catechin	-10.6	
	Taiwanhomoflavone A	−9.6	

Table 6. *Cont.*

Target/Binding Site	Natural Products/Metabolites	Binding Energy (kcal mol^{-1})	Reference
TMPRSS2	Isogemichalcone B	−13.07	[184]
	Microcarpin	−13.31	
	Durumolide K	−13.92	
	Dictyosphaeric acid A	−14.02	
	Geniposide	−14.69	
	Baicalin	−8.46	[198]
	Silybin	−11.928	[190]
	Tetrahydrocurcumin	−8.793	
	Corydine	−7.91	
	Aloin	−9.18	
HSPA5	Caffeic acid	−6.2	[199]
	Chlorogenic acid	−6.5	
	Palmitic acid	−5.5	
	Biochanin A	−6.9	
	Formotein	−7.5	
	Genistein	−7.5	
	Diadiazin	−8.6	
NSP1	Shogaol	−2.64	[200]
	Gingerenone	−4.39	
	Remdesivir	−5.8	
	Lactose	−11.66	
	Esculin	−6.88	
	(-)-Epicatechin 3-O-(3'-O-methyl) gallate	−13.1	[184]
	Curtisian L	−13.38	
	5-Methoxyhydnocarpin	−13.92	
	Citicoline	−13.96	
	Isoaloresin	−9.759	[190]
	Withaferin A	−11.242	
	Hinokinin	−7.67	
	Philligenin	−9.503	
	Excavatolide M	−14.38	[184]
	Schisphenin A	−14.27	

Red color: a repurposed drug used as control.

12. Obstacles to Research on COVID-19 Pathogenesis

Animal models serve a critical role in unveiling pathogenicity mechanisms of the virus, from the entrance to the transmission, and targeting therapeutic strategies. Earlier, to check the replication of SARS-CoV-2, symptoms of serious infections were depicted by different animal models [201]. In small animals, MERS-CoV pathogenesis was not observed in contrast to SARS-CoV-2. As a result of the non-compatibility of the DPP4 receptor, mice are not at risk of infection with MERS-coronavirus [202]. The infectious pathogenicity

of SARS-CoV-2 can be determined by the animal models as used in SARS-CoV-2 since both the viruses share 80% of the genomes and recognize ACE2 receptors. Hamsters that have been genetically modified with CRISPR or TALEN or other small animals can be used for studying the novel coronaviruses' pathogenicity. Replication of SARS-CoV-2 has been reported as a cause for severe ailments in rats (f344), wherein at spike glycoprotein, a mutation was revealed by the sequence analysis [203]. Therefore, it can emerge as a suitable alternate option for the development of spike glycoprotein targeting therapeutics against novel coronaviruses. Clinical isolates and mice models were used recently for the development of a therapeutic strategy against COVID-19 induced by SARS-CoV-2 [111,152]. Artificial Intelligence prediction has also been used in a similar study for investigating the drug's inhibitory role against SARS-CoV-2 [153]. Randomized clinical trials were also conducted on patients suffering from SARS-CoV-2 [147,151,152]. The investigation into the *invivo* mechanisms relevant to the pathogenesis of COVID-19 mandates the global collaboration of scientists for designing an appropriate model.

13. Conclusions

The sudden sprouting of COVID-19 cases across the globe has questioned the solidarity of the medical fraternity. Apart from lungs, viral infections-mediated inflammatory state and immonumodulation may have potentially adverse impacts on several other organs/organ systems, too [204,205]. The sudden outset of this viral infection has brought people into captivity across the nations. The day-to-day altering trends in symptomatology and presentation have pacified the molecular research and developmental sciences to come up with safer and effective therapeutic agents and vaccines. To date, we are comprehending and battling this pandemic with no proven therapeutics. The need of the hour is to consider a holistic approach and render supportive care, as per the presenting severity of the case. While combating a pandemic, it is of utmost importance for health care professionals to keep themselves updated with the current and emerging therapeutic trends for treating the disease with greater effectiveness [206–210]. A multidisciplinary team must mitigate the secondary waves of the pandemic with all the necessary precautions. At the same time, it is equally important to optimize novel ideology of cellular therapy protocols in adjunct to the development of vaccines, as these have the potential to prove as the positive shades of a rainbow amidst the storm of COVID-19 pandemic. Further research on the definitive management protocols by conducting randomized controlled trials is greatly needed for the hour because safety and efficacy parameters need to be concretely investigated.

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