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Coronavirus Disease (COVID-19), Chemical Structure, Therapeutics, Drugs and Vaccines

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Abstract: Biochemistry has the main role to play in understanding the structure of viral to develop techniques and materials used by clinicians, virologists, and researchers, as well as isolation of therapies and vaccines. Biochemistry helps to understand the molecules that manage virus structure and function can accelerate discovering means to treat and avoid infectious disease. The significant contributions of biochemistry are providing to understanding and monitoring the spread of coronaviruses. COVID-19 is a novel type of coronavirus influence humans and was recognized in 2019. The terms severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), 2019 novel coronavirus, and COVID-19 mention the same virus. All present medication choices are based on experience with MERS, SARS, and other new influenza viruses. Thus, it is essential to understand the virus structure and its clinical features to respond to the COVID-19 outbreak. Intensive studies are currently being carried out to develop specific drugs or vaccines for the COVID-19 coronavirus. This study will shed light on the various present and future research efforts to treat the COVID-19 by evaluating past studies to assist the therapeutics for COVID-19 improve quickly.

Keywords: Coronavirus 2019-nCoV; diagnosis; COVID-19; viruses; infectious diseases.

1. Introduction

The COVID-19 is the name given to the 2019 novel coronavirus, and it is a novel strain of coronavirus [1,2]. Formerly, six coronaviruses (CoVs) are recognized to cause diseases in humans, and these can be defined as low, highly pathogenic CoVs [3,4]. According to the World Health Organization (WHO), the WHO China Office reported pneumonia of unknown etiology in Wuhan City at the end of 2019 [5,6]. The Chinese authority of the health [7] showed that the patients primarily tested negatively for the viruses and respiratory bacteria but later tested positive for a new coronavirus [8–10]. The virus was presently isolated and its genome sequenced by Chinese scientists [11]. In February 2020, the coronavirus disease 2019 was selected as the disease COVID-19 by WHO [12]. The COVID-19 can cause infections in different animals and most infections of the respiratory tract in individuals, including the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) [13,14].

The COVID-19 virus is completely different from the viruses accountable for SARS and MERS [15,16]. The COVID-19 genome sequences got from the patients part a 79.5% sequence related to that of SARS-CoV [17,18]. The signs and symptoms characteristically occur among two weeks after contact and consist of fever, coughing, respiratory disorders, pain in the chest, and trouble breathing [2,19]. Possibly deadly complications include pneumonia and kidney failure [20,21].

As on December 30, 2020, a total number of 82,739,879 cases of COVID-19 (with 1,804,879 deaths) have been reported from 191 countries worldwide according to the WHO situation report. United States of America as epicenter of the current COVID-19 reported maximum deaths associated with COVID-19 (20,034,309 laboratory confirmed cases with 347,713 deaths). The countries where more than 2,000,000 people are affected include India(10,264,426), Brazil (7,577,890), Russia(3,131,550), France (2,600,498), England (2,432,888), Turkey (2,194,272) and Italy (2,083,689) [12].

In the present development, the United States of America and most European nations bear the brunt of the burden of illness and death associated with COVID-19 relative to other nations [12]. The latest increase in consistently reported patients with COVID-19 has now reached acute care stocks, restricting acute care coverage to just a limited percentage of critical patients. This may also have led to the elevated fatality ratio found during the COVID-19 outbreak.

2. Chemical structure of COVID-19

Coronaviruses encode four main structural proteins, namely Envelope (E), Membrane (M), Nucleocapsid (N), and Spike (S), which are defined in feature as below.

2.1. Nucleocapsid (N)[N protein].

There are multipurpose of the N protein of coronavirus. It supports the formation of the complex with the genome of viral, enables the interaction of M protein through virion assemblage, in addition to increases transcription efficiency of the virus [22,23]. There are three extremely distinct and conserved domains, namely a linker region (LKR), an N-terminal domain (NTD), and a C-terminal domain (CTD) [24]. The charged LKR is rich with arginine and serine and is also recognized as SR (Serine and Arginine) domain [25]. The LKR region is responsible for the cell's signaling and is also able to interact with *in vitro* RNA directly [26]. The NTD binds with the 3' end of the viral genome, probably by its highly splay in the sequence and length and electrostatic interactions [26]. Compared to SARS-CoV, the N protein of COVID-19 has five amino acid mutations, wherever the two mutations are in the intestinally distributed region, one in the 103, 217, and 334 positions of NTD, LKR, and CTD, respectively [27].

2.2. Envelope (E)[E protein].

The role of protein E in pathogenesis and virus release is multifunctional. It is the most mysterious and lowest among the main structural proteins [27,28]. It is a small integral polypeptide membrane that functions as an ion-channel. The E protein contains three domains: an excellent C terminal domain, a large hydrophobic transmembrane domain, and a short hydrophilic amino-terminal domain. The E protein of COVID-19 exposes a similar amino acid composition without any change [27].

2.3. Membrane (M) [M protein].

The Membrane (M) (M protein) is highly varied concerning amino acid contents. It is the most bountiful viral protein present in the virion structure, giving the viral envelope a distinct form. It binds to nucleocapsid and acts as the central organizer of coronavirus assembly [29]. The M protein has three transmembrane domains, flanked by a long carboxy-terminal inside the virion short amino-terminal outside the virion [30]. Generally, the viral framework is conserved by M-M interaction. In the study made by Wu *et al.*, the M protein of COVID-19 does not have any amino acid substitution compared to the SARS-CoV [27].

2.4. Spike (S) [S protein].

The coronavirus spike (S) or [S protein] is a multifunctional class I transmembrane protein. This rests on the top of the virion like a trimmer, giving the virion a 'corona' or crown-like outer look. Operationally, interaction with cellular receptors of various kinds is necessary for the entry of infectious virion components within the cell [31]. Moreover, it works as a significant feature for tissue tropism [30]. Particularly, S protein is a single vital immune dominant protein of coronaviruses that prompt the host immune response. The S protein of all coronaviruses is divided into two domains [32]. Initially, S1, facilitates the binding of host receptors while the other, S2, is responsible for the fusion. Already, the structural study of COVID-19's S-proteins exposed 27 amino acid substitutions over a period of 1273 amino acid stretches [27,29]. Inter the six substitutions, placed in the receptor-binding domain (RBD) (aa 357-528) while four substitutions in the receptor-binding motif (RBM) at the CTD of the S1 domain. There is no shift in amino acid in the RBM that binds directly to the angiotensin-converting enzyme-2 (ACE2) receptor in SARS-CoV [33]. It is currently important to identify how many changes will be essential to alter the host's tropism. The evaluation of sequence exposed 17 non-synonymous variations in the primary sequence of SARS261 CoV-2 than the later isolates of SARS-CoV, as shown in Figure 1(A-C). The modifications were located distributed in the open reading frame (ORF) 1ab, ORF8 (4 substitutions), spike gene (3 substitutions), and ORF7a (single substitution) over the genome of a virus with 9 substitutions [34]. Particularly, the same non-synonymous modifications were detected in a familial group showing that the viral evolvement might have happened throughout person-to-person transportation [35,36]. Such adaptive evolvement is public and constitutes a constantly ongoing process once the spread of virus between new hosts [31,37]. Despite this fact, no changes in the functional occur in the virus associated with this adaptive development. Observing the viral mutations that happen throughout subsequent human-to-human transmission is verified [38,39]. Fusion Animation has shaped a 3D model of the COVID-19 surface as a new model for use in drug development. The model was created by assembling 3D parts related to structures of COVID-19 coronavirus accessible in open databases. The previous study presented that the M protein exposed is complexed with human leukocyte antigen serotype. The protein distribution on the virus surface was aligned by a random process [28]. The general picture surface protein density has been summary to assistance show M, E, and S proteins. A particle system created the M lipid itself to yield a random and organic result, Figure 1D [40].

3. Physicochemical Features.

The virus particle diameter has around 60~100 nm with a round or oval shape [42]. The COVID-19 can be inactivated by heating at 56 ºC 30 min or by using UV, and sensible to many disinfectants like ethanol (75%), acetic acid, diethyl ether, and chlorine. It has been described that COVID-19 was more stable on stainless steel and plastic than copper [43].

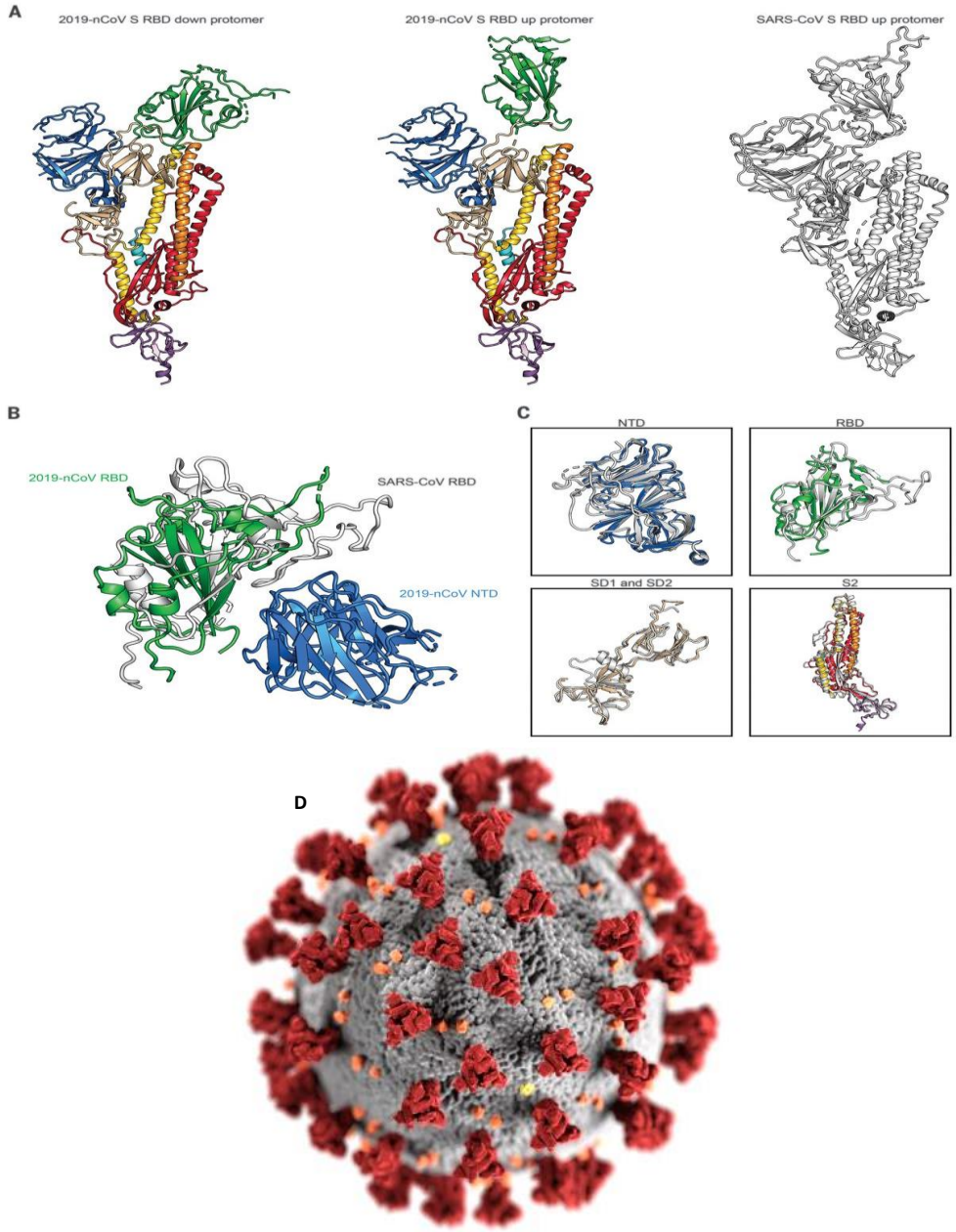

Figure 1. Structural comparison between COVID-19 (2019-nCoV S) and SARS-CoV S**. (A)** Single protomer of COVID-19 with the RBD in the down conformation. COVID-19 protomer in the RBD is exposed (center) following to a protomer of SARS-CoV S in the RBD up (right), shown as stripes and colored white.;**(B)** RBDs of COVID-19 and SARS-CoV aligned based on the position of the neighboring NTD from the neighboring protomer; **(C)** Structural domains from COVID-19 S have been aligned to their complements from SARS-CoV S [41]; **(D)** A representation of three-D of the COVID-19 surface [40].

4. Cell Entry and Receptor Connections

The angiotensin-converting enzyme 2 (ACE2) in humans is a receptor appropriated by COVID-19 for cell access, like SARS-CoV[32]. ACE2 is a type I membrane protein in the heart, lung, intestine, and kidney generally connected by heart illnesses. ACE2 contains an N-

terminal peptidase domain and a C terminal Collectrin-like domain that ends with a single transmembrane helix and an around 40-residue intracellular fragment [43]. Furthermore, the ACE2 can bind directly with the S proteins of CoVs to split angiotensin (Ang) I to generate Ang-(1-9) [44].

The CoVs S protein is a metastable prefusion validation that undergoes a remarkable structural reorganization to fuse the viral membrane with the host cell membrane [45]. Reasonable to find out COVID-19's capacity for infecting humans, the RBD of its S-protein, which interacts with ACE2, has been examined. The structural and biophysical evidence confirmed that COVID-19 S-protein is likely to bind more than 10-20 fold higher affinity to human ACE2 than SARS-CoV [41]. Another structural suggestion proposes that the ACE2-B0AT1 complex can bind two S-proteins concurrently [46,47].

The COVID-19 is an envelope with positive-sense, single-stranded RNA beta coronavirus [48,49]. The genome of the CoVs, ranging in length from 26-32 kilobase, is possibly the major viral RNA identified [50]. Similar to SARS and MERS, the genome of COVID-19 encodes structural proteins (for example, spike glycoprotein), non-structural proteins (for instance, 3-chymotrypsin-alike protease, helicase, and papain-alike protease), and accessory proteins. Functionally important ORF1a and ORF1b, On the other hand, the interrelationships of functionally important ORF1a and ORF1b and other principal structural proteins such as E, M, N and S proteins are also extremely good and are clearly shown in Fig. 2. While the E and M proteins are necessary for the assembly of the virus into host cells, it has been stated in the literature that the affinity of the S protein is very important for binding to the host cells, as the RBD of the S protein provides binding with ACE2 [51].

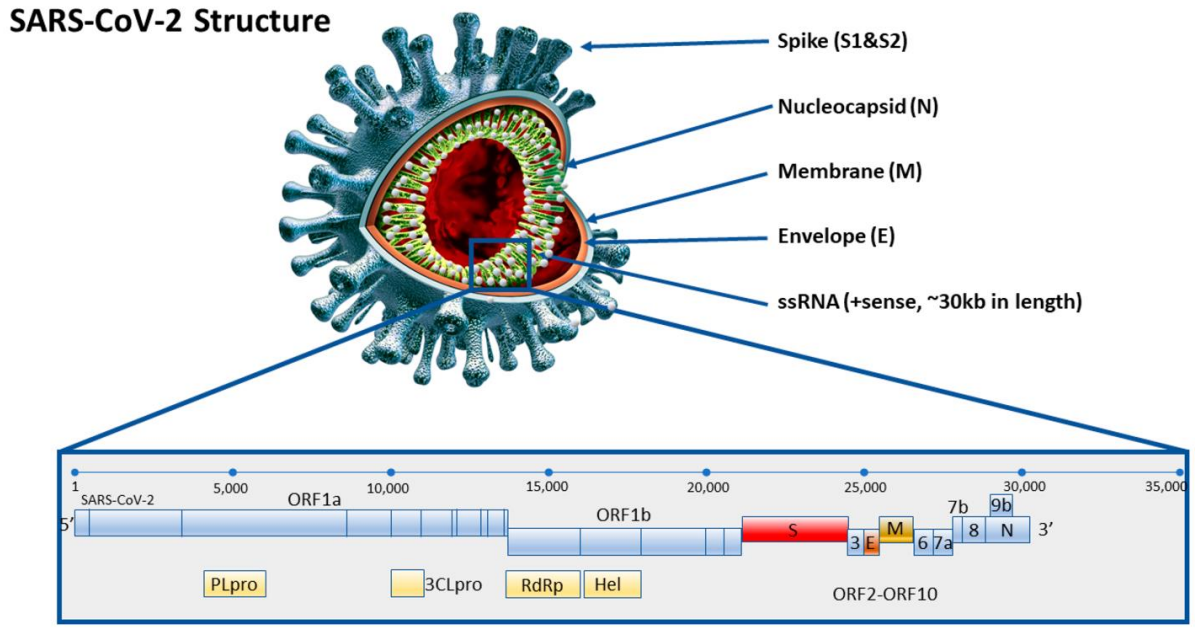

Figure 2. Organization of COVID-19 genome [51].

Liu *et al.* showed that the COVID-19 spike RBD is notably dissimilar from the SARS-CoV spike RBD, mainly in the regions which bind to the ACE2 (Figure 3). This modification efficiently removes the use of formerly therapeutic peptides and industrialized antibodies for the SARS-CoV. A probable rapid remedy to suppress the RBD–ACE2 interaction to stop the infection is to produce peptides reproduced from RBD and ACE2 and concoctions thereof [52].

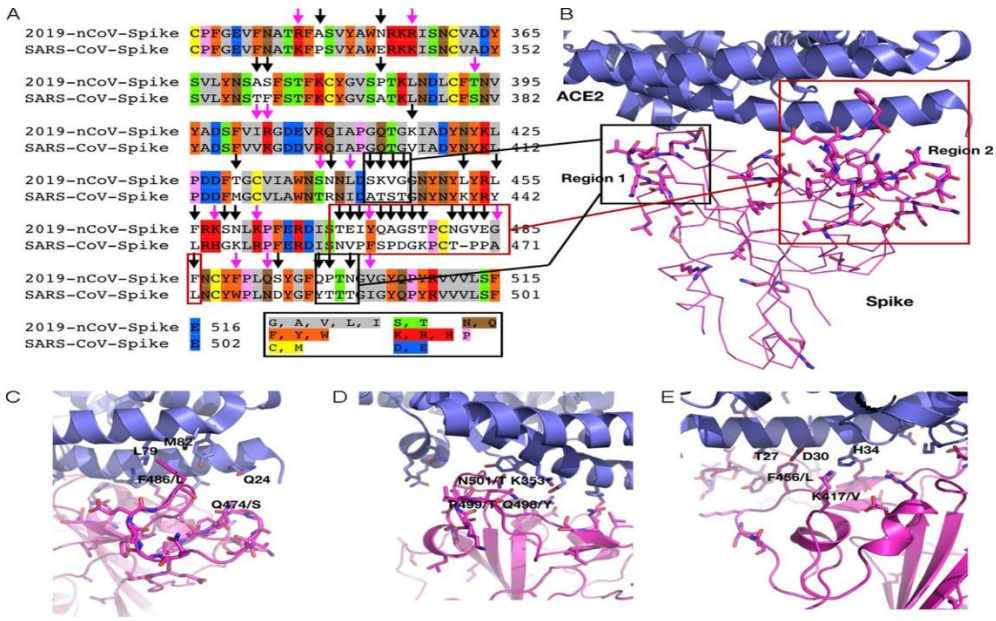

Figure 3. (A) Amino acids sequence position in the COVID-19 and SARS-CoV spike domains. Preserved (pink arrows) and nonconserved (black arrows) mutations are highlighted. (B)Numerous binding connections between the COVID-19 spike protein (pink) and ACE2 (blue; spike protein homology).(C–E) Zoomed in views of some spike protein-ACE2 interactions described in (B) [52].

In type 2 alveolar epithelial cells surface of lungs, the ACE2 is displayed within the renin-angiotensin system (RAS) [53,54]. The ACE2 is a significant regulating factor of the RAS and shares around 60% homology with ACE [55]. The ACE2 converts (Ang) II into Ang-(1-7), which actions on the Mas receptor, expressed on a cell lineage in numerous tissues pertinent to cardiovascular illness to discreetly lower blood pressure over vasodilation and by secretion of water and sodium from kidney, moreover produce nitric oxide to reduce inflammation [56,57].

There are two theories to clarify the conflicting hypothetical pathways by which the inhibition of RAS with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin-receptor blocker (ARB) can be injurious or protective in COVID-19 [58,59]. The first one supposes that severe acute respiratory COVID-19 improves its entry into the cell by binding to ACE2. The addition of an ACEi or ARB could increase the abundance of the ACE2 and increase the viral entry. The second hypothesis assumes that (Ang II) causes the lung's injury by activating the type 1 angiotensin receptor (AT1R), initiating the infection and fibrosis. The decrease in the production of Ang II with an ACEi or obstructive action of Ang II–AT1R with an ARB improves the formation of Ang-(1–7) by ACE2 and of the Mas receptor activity, which leads to a decrease the lung inflammatory and fibrosis and consequently reduces injury of the lung [53,60].

5. COVID Diagnosis

For COVID-19, virus-specific antibodies can be monitored from the serum/plasma sample. IgM antibody begins to become positive on days 3-4 of the symptoms or days 7-10 of infection and IgG antibody on days 11-14 of the infection. Seroconversion has been shown to occur in 50% of patients on days 7 and 14 in all patients.

6. COVID-19 Treatment

In general, there are different approaches used together in CoVID-19 treatment, and in these approaches, drug compounds can be selected according to virus-based and host-based treatment [61,62]. The first process offers broad-spectrum antiviral drugs, previously used to treat viral infections by typical assays. These drugs' effects on pseudo coronaviruses, cytopathic, viral production, and living cells plaque formation can be measured in these approaches. This method contains interferon I and interferon II [63,64]. These drugs have pharmacodynamic and pharmacokinetic features with their drug regimens and side effects [20,65]. On the other hand, the anti-COVID-19 virus has no specific effects and can be related to extreme opposite reactions. The second process includes improving exact novel drugs created on the biophysical and genome understanding of the COVID-19 virus patients. The method includes an inhibitor of the host cell endocytosis virus, inhibitors targeting specific viral enzymes found in a viral replication cycle, inhibitors of the host cell's protease enzyme, targeting human-derived or humanized monoclonal antibodies (mAb) S1 RBD, and antiviral targeting peptide S2. On the other hand, the improvement of these drugs may permit drugs to become beneficial treatment choices, but it will take a long time to supply dependable drugs for COVID-19 virus patients [66,67]. The chief problem of this method is that though most of the recognized drugs display *in vitro* anti-coronavirus activity, the greatest of them are not beneficial in clinical treatment because they have half the EC50 value of the anti-coronavirus, which is considerably higher than the concentration of peak serum that can be performed at the treatment dose or associated with immunosuppression [11,68]. The third process includes the publication of a chemical library with various compounds or databases containing knowledge about the properties of transcription for different cell lines [69]. This process may provide fast and high yields for many simply obtainable compounds and then estimate them with an antiviral test. Several drugs with significant immunological and physiological effects such as kinase signal transduction, an estrogen receptor, DNA synthesis or repair, lipid, and protein metabolism have been recognized in these drug reuse programs [70,71]. The fourth process also includes treatment methods used by Acupuncturists with a meaningful result in the management of patients with COVID-19. One hypothetically effective method is a synthetic form of quinine, called hydroxyl chloroquine [72–74]. Presently, malaria is treated with natural and synthetic forms of the Chinese herbal medicine Qing Hao. On the other side, Cortegiani *et al.* found that chloroquine appears to be effective in reduced the replication of COVID-19 *in vitro* [74]. Furthermore, Gao *et al.* showed that chloroquine is significantly effective compared to a control group in 100 patients for symptoms duration, decreasing pneumonia exacerbations, and viral clearance postpone. Also, this study displayed that chloroquine might decrease the length of hospital stays [75]. Chloroquine and oxygen treatment is recommended by the Infectious and Tropical Disease Society and the Dutch Centre for Disease Control in Italy, with separate dosage guidelines compared with the Chinese Protocol. Colson *et al.* conclude that sufficient preclinical indication is available for the chloroquine used in COVID-19 treatment [76].

In 2003, Chinese medicine had been used in the same disorders during the SARS outbreak, with recognized clinical successes [77]. Despite primary clinical achievements and hopeful research, the treatment rate for COVID-19 remains difficult to succeed. The herbal formula Qing Fei Pai Du Tang had a reply rate of 90 percent of a total of 214 clinical cases of COVID-19 related pneumonia, with respect to the National Administration of Traditional

Chinese Medicine [77,78]. Patients were treated in the provinces of Shanxi, Hebei, Shanxi, and Heilongjiang during this clinical research. A description of the response rate of 90% is as follows: symptoms changed dramatically in around 60% and the remaining 30% stable [79]. Another research surveyed 701 COVID-19 patients in ten Chinese cities who received Qing Fei Pai Du Tang medication. A total of 130 patients (18.5%) were cured, symptom changes were achieved in a further 268 patients (38.2%), and recovery occurred in 212 patients (30.2%). Other studies showed that Lian Hua Qing Wen Capsule decreased the COVID-19 symptoms and upgraded healing [80–82]. Besides, the Lianhuaqingwen Capsules and Shu Feng JieDu Capsules have played a significant role in treating infectious diseases like influenza A (H1N1) [83]. Conversely, the safety and effectiveness of these drugs in COVID-19 require to be more validated vi clinical tests.

Furthermore, nucleoside analogs may have numerous action mechanisms, including chain termination, lethal mutagenesis, and nucleotides' biosynthesis inhibition [84–86]. The tribavirin and favilavir are nucleoside analogs representatives, which pooled with Avigan and oseltamivir in acute influenza care are superior to oseltamivir only [87]. On the other hand, the Neuraminidase inhibitors such as zanamivir and oseltamivir are suggested as antiviral treatment in infection [88]. The oseltamivir has been commonly used for COVID-19 in China. The chiefly point for patients is the beginning of antiviral medication immediately after disease initiation. It has revealed that neuraminidase inhibitors are more active in MERS-CoV infection, but there is no significant indication that oseltamivir is influential in COVID-19 care.

Moreover, Remdesivir may be the possible drug for the care of COVID-19. The experiments in animals exhibited that effectively decrease the virus titer of mice infected with COVID-19 comparing to healthy mice, decrease the damage of the lung tissue [89]. Conversely, the safety and efficiency of Remdesivir in patients with COVID-19 still need more clinical research. Presently, other types of drugs have been starting to be influential *in vitro*, like fusion peptides, RNA synthesis inhibitors, and anti-inflammatory drugs [90].

In Turkey, in the first Covid-19 cases encountered, it was taken into account the accumulation of experiences and treatment protocols of China, previously living the process of combating the pandemic. But after the first 1-2 weeks, Turkey has developed its treatment algorithm based on its own clinical observation and experience. Furthermore, the Ministry of Health also made updates to the algorithm according to the developments within the framework of the recommendations of the Scientific Board established after the Coronavirus outbreak. In Turkey, a dissociated and effective treatment protocol was formed differently from other applications in the world. The strategies developed in the light of the objective recommendations of the Scientific Committee based on scientific data, the professional experience of healthcare professionals who implement these strategies, their organizational capabilities, well-equipped and extensive hospital infrastructure and the capacity of intensive care units with high-quality equipment above the world average was formed a great advantage in combating Covid-19 [68].

- Since the Ministry of Health has sufficient drug stocks, hydroxychloroquine treatment was started at the early stage of the disease.
- Favipiravir treatment was started when replicating the virus, that is, before the disease gets seriously worse, before the need for intensive care. Whereas in the first applications, it was started in the intensive care process, this is an application that has been put into practice in the intensive care stage of the disease in many countries still, but it is thought that it is not very effective at this stage.

- It was given up from early intubation (invasive ventilation) in intensive care patients. Because it was observed that this did not change the course of the disease much. Non-invasive ventilation technique (continuous positive pressure airway (CPCA)) has begun to be used instead of invasive ventilation, which is insufficient. Thus, the risks of lung damages caused by invasive ventilation were also prevented.
- It was also observed that the disease was not a typical ARDS table as described, additional problems such as coagulopathy (coagulation disorder) also occurred, and patients were also lost due to this reason. Accordingly, anticoagulant drugs have also affixed the algorithm.
- For the diagnosis of Covid-19, the capacity of quantity and quality of IT, present in hospitals in Turkey, more effective than PCR, has increased its capability for rapid diagnosis.

In the cure of Covid-19 patients in Turkey, the following protocols were applied after grouping patients. Mild, possible/definitive Covid-19 outpatient case treatment; hydroxychloroquine and oseltamivir therapy was recommended for 5 days period for patients with mild symptoms, under 50 years of age, pneumonia and concomitant hypertension, cardiovascular diseases, chronic airway disease, diabetes, cancer, immune suppression and patients with undiagnosed/influenza [91]. Moderate, possible/definitive Covid-19 service treatment; it was recommended to azithromycin addition for 5 days to hydroxychloroquine and oseltamivir therapy for the cure of patients [75,92], who need hospitalization, but do not have a pneumonia picture and clinic heavy and do not have accompanying comorbid diseases, and the cases in the middle clinic [91,93]. Serious, possible/definitive Covid-19 case treatment; it was recommended to use favipiravir for 5 days, which is an effective antiviral in the management of patients with acute pneumonia, concomitant comorbid diseases, and severe clinic, and to add favipiravir to the treatment of patients who worsen the clinic while taking hydroxychloroquine treatment in cases of mild disease, and develop pneumonia. The following suggestions can be made for treatments in some special cases by the experience gained during the treatments in Turkey. According to clinical, laboratory, and radiological findings, among those who started Covid-19 treatment, it is known that it is appropriate to add drugs such as quinolone to the effective atypical agents' beta-lactam antibiotics to those who are considered to have infection/pneumonia [33,91].

Inhaler drugs that should be given with nebulizer should be administered with a metered-dose inhaler due to the risk of transmission. In non-invasive mechanical ventilation (NIMV) applications, the mask should be preferred for reducing infectious. It is recommended to evaluate the option of follow-up without treatment if the symptoms/clinic are mild, if comorbid conditions are not accompanied in pregnant women with Covid-19 definitive diagnosis, to use treatment Lopinavir 200 mg/ritonavir 50 mg tb 2x2 10/14 days orally and to add hydroxychloracine 5 days depending on the situation. Favipiravir should not be used in nursing mothers and pregnant women [91].

There is concern about the use of nonsteroidal anti-inflammatory drugs (NSAIDs) [19]. This concern has evolved because several young patients used NSAIDs in the early phase of the disease, and their condition deteriorated. However, currently, there is insufficient data to support NSAID use or to ban it altogether. For suspicious cases, acetaminophen should be preferred as an analgesic and antipyretic. In all Covid-19 patients who are hospitalized for the prevention of venous thromboembolism, prophylaxis is recommended using low molecular weight heparin if there are no contraindicated conditions such as active bleeding and severe

thrombocytopenia. In intensive care patients whose clinic worsens while lying in the service, the addition of steroid 1-2 mg/kg/day 5-7/day and high dose of vitamin C, 25 g/day, according to the clinical condition of the patients, the addition of IL-6 inhibitor tocilizumab in patients with cytokine storm findings, should be evaluated [91].

Immune plasma therapy and stem cell therapy have been begun to use as promising treatments in patients whose general condition has deteriorated and did not respond to treatment [94,95].

Since SARS-CoV-2 is a newly encountered virus, no vaccine, monoclonal antibody, or a drug that directly affects it has been developed yet. Although there are promising studies on vaccine and drug development, there is a high probability of not being completed for this pandemic period. Therefore, one of the fastest and easiest treatment options that first comes to mind and can directly target SARS-CoV-2 is to take serum or plasma from people who have survived this disease and are considered to contain antibodies against this virus and use it for both preventive and therapeutic purposes. Serum or plasma treatment has started to be easier and find application area by increasing the number of those who survived the disease. Unlike the vaccine, this use falls into the class of passive antibody therapy (PAT) and includes benefits and risks [68,91].

Considering the previous experience with plasma treatment, it seems to be the only available treatment option for the Covid-19 pandemic in today's conditions where vaccines and drugs could not be developed. One of the most important factors in the positive outcome of this treatment can be summarized as the presence of sufficient neutralizing antibodies in the transplanted plasma, and another is the rapid start of treatment of individuals with potential risk factors such as age. Briefly, since the recovered patients' immune systems reacted differently to the virus, treatment should be directed considering the possibility of not having enough antibodies or not at all, if very few [1,96]. In the treatment to be performed 1 week after the first plasma treatment, it is more appropriate to give the plasma of another donor or the plasma from a few donors to the patient. This is valid for the current situation, but it is expected that an efficacy test will be carried out before it is given for neutralization in the future. The PAT carries several risks. There can also be an enhanced risk of antibody-dependent viral infections, and its molecular mechanism is unknown. Besides, there is another risk that antibody therapy will suppress the development of acquired immunity. While this situation requires that the antibody level in the treatment of PAT is sufficient until the disease is completely eliminated, it should be considered that an immune memory cannot be formed due to the metabolism of the externally given antibodies [91,97].

Consequently, the vaccine should be taken into account after PAT. In addition, the duration of the plasma antibody and the duration of effectiveness of this acquired immunity are also important as additional information [98]. In this pandemic era, it is expected to pay attention to the vaccination of individuals who are not yet immune, rather than vaccinating individuals who have naturally active antibody counts [91,99].

It is not known how it will affect the people who got and survive this disease in the long term [98]. The 'COVID-19 Patient Monitoring Center' was opened by the Istanbul Medical Faculty to answer these questions. This center will investigate whether the coronavirus causes permanent damage in patients by performing various tests and examinations on those who got coronavirus and survive [100]. While struggling with this disease, some problems were observed in organs such as the lungs, heart, intestines, and liver. Some publications were started to be discussed in the literature; some question marks whether these problems will continue,

especially whether lung, liver, or kidney problems will be carried in the long term [94,101]. Thereupon, 'COVID-19 Patient Monitoring Center' was established in Turkey, and this center is the first center in Turkey and the world for this goal. For patients who have had severe COVID-19 infection, some problems that may occur by following them at 1, 3, 6, 9, and 12th months after their treatment will be diagnosed and treated at this center [102].

7. Vaccine Development for COVID Treatment

Although there is no whole and complete treatment for COVID-19 yet, two treatment strategies have gained priority: the first is to rearrange and use previously approved pharmacological agents, and the second is to develop new treatment strategies to reduce the ever-spreading virus-related morbidity and mortality. The second strategy is to prevent further spread and relapse in society. For this purpose, the advancement, controlling production, and delivery of an effective and secure vaccine with scientists' contributions as a long-term solution proposal will reach everyone as soon as possible [103].

7.1. Non-replicating viral vectors (NRVV).

Adenoviral-based candidates are widely used for non-recurrent SARS-CoV-2 vaccines. Adenoviruses are characteristic double-stranded DNA viruses that inactivate replication by deletion of the E1 regions. Upon infection of target cells, there is an up-level transgene expression and upregulation of costimulatory molecules that chemokine responses and elicit cytokine, enhancing immunogenicity. SARS-CoV-2 is thought to use the S-protein to enter cells, so all vaccines in current trials contain either the S-protein subunits or the full-length S-protein [103].

7.2. Messenger RNA vaccine candidates.

Hitherto, there is no FDA-approved mRNA vaccine for humans, but considering the extra conditions brought by the COVID-19 global epidemic, mRNA vaccine studies are being tried as a new method. Since the production of nucleic acid vaccine candidates is faster and cheaper than protein subunit vaccines, a few mRNA-based SARS CoV-2 vaccine candidates have been developed and are recently being tested. Traditional mRNA vaccine design generally includes an open reading frame of the targeted antigen (spike protein for SARS CoV-2) with a 3′ polyadenylated tail that generates both humoral and cellular immune responses. The degradation tendency of mRNA has been a major barrier to mRNA vaccine development; Therefore, stability and proper intracellular mRNA translation are of paramount importance for achieving these vaccine candidates. Miscellaneous methods have been advanced to overcome these issues, such as extracting double-stranded RNA and buried mRNA in lipid nanoparticles [103].

7.3. Self-amplifying messenger RNA vaccine candidates.

With the latest technological approaches, self-amplifying RNA (saRNA) vaccines have been advanced in extension to non-amplifying mRNA vaccines. Trinidad ass, these vaccines are highly promising as they have the potential to induce a stronger immunological response than a non-replicating mRNA vaccine, although this is a significant downside given their RNA sequence content for the protein [103].

7.4. DNA vaccine candidates.

DNA-based vaccine candidate has many superior properties, such as the DNA molecule's stability compared to RNA, and the ability of DNA structures to generate a large number of mRNA molecules, thereby increasing the immunological exposure of a DNA-based vaccine target antigen. In addition to all these advantages, DNA-based vaccines have less cooling requirement than their mRNA-based response due to the thermal stability of DNA [103].

7.5. Inactivated whole-virus vaccine candidates.

Although the vast majority of successful vaccines in the historical period are vaccines that induce immunity using inactivated pathogens, the prolonged production of such vaccines has reduced the possibility of using inactivated full virus vaccine candidates in the COVID-19 pandemic. In proportion to other genres of vaccines, inactivated viral vaccines have fewer side effects, and most of the systemic side effects are mild, including localized rash and pain at the injection site [103].

7.6. Protein subunit vaccine candidates.

The synthetic protein subunit approach is an alternative vaccine generation method between nucleic acid-based mechanisms and inactivated complete virus vaccines, which part of SARS-CoV-2 vaccine candidates includes a recombinant spike protein expressed in various cell lines. Similar to RNA-based approaches in protein subunit vaccines, peptides are often unstable in vivo and are typically packaged in nanoparticles adsorbed onto specific adjuvants structured to increase the protein cargo's uptake into host antigen-presenting cells [103]. Vaccines attempted to be developed for SARS-CoV-2 are summarized in Table 1.

Table 1. Short-form list of SARS-CoV-2 vaccines in human clinical trials of Phase ≥2.

GENRE	ESTABLISHMENT	CLINIC PHASE	PROPER NAME	REGISTRY INDEX	REFERENCES
INACTIVATED VACCINES	Institute of Medical Biology, Chinese Academy of Medical Sciences	1/2	Inactivated SARS-CoV-2 Vaccine	NCT04470609	[103, 104]
	Research Institute for Biological Safety Problems, Republic of Kazahstan	1/2	QazCovid-in®	NCT04530357	[103]
	Bharat Biotech (Whole Virion Inactivated)	1/2	BBV152A/B	NCT04471519	[103]
	Beijing Institute of Biological Products/Sinopharm	1/2	Inactivated	ChiCTR2000032459	[104]
	Bejing Institute of Biological Products/Sinopharm	3	BBIBP-CorV	NCT04560881 ChiCTR2000034780	[103, 106]
	Wuhan Institute of Biological Products/Sinopharm	3	Inactivated COVID-19 vaccine (Vero cells)	ChiCTR2000034780	[103, 106, 107]
	Sinovac	3	CoronaVac/PiCoVacc	NCT04456595NCT0458234	[103, 106, 107]
NON-REPLICATING	CanSino Biological Inc./Beijing Institute of Biotechnology	2	Adenovirus Type 5 Vector	ChiCTR2000031781	[104]

GENRE	ESTABLISHMENT	CLINIC PHASE	PROPER NAME	REGISTRY INDEX	REFERENCES
VIRAL VECTORS	Cansino Biological Inc./Bejing Institute of Biotechnology	3	Ad5-nCoV	NCT04526990NCT04540419	[103, 106, 107]
	University of Oxford/Astra Zeneca	3	AZD1222 (ChAdOx1 nCoV-19)	NCT04516746NCT04540393	[103, 106]
	Janssen Pharmaceutical Companies (Johnson&Johnson)	3	Ad26.COV2·S	NCT04505722	[103, 107]
	Gamaleya Research Institute	3	Gam-COVID-Vac	NCT04530396NCT04564716	[103, 106, 107]
	University of Oxford	1	ChAdOx1 MERS	NC03399578	[105]
	ReiThera/ LEUKOCARE/ Univercells	1	GRAd-CoV2	NCT04528641	[105]
	Institute of Biotechnology, Academy of Military Medical Sciences, PLA of China	1	Ad5-nCoV	NCT04552366	[105]
	Vaxart	1	VXA-CoV2-1	NCT04563702	[105]
	ImmunityBio, Inc./ NantKwest Inc.	1	hAd5 S+ N	NCT04591717	[105]
	Ludwig-Maximilians--University of Munich	1	MVA-SARS-2-S	NCT04569383	[105]
	City of Hope Medical Center	1	COH04S1	NCT04639466	[105]
REPLICATING VIRAL VECTORS	Themis Bioscience	2	MV-CHIK	NCT02861586	[105]
	Institut Pasteur/ Themis/ University of Pittsburgh CVR/ Merck Sharp & Dohme	1	TMV-083	NCT04497298	[105]
	Beijing Wantai Biological Pharmacy/ Xiamen University	1	DelNS1- 2019-nCoVRBD- OPT1	ChiCTR2000037782	[105]
	Israel Institute for Biological Research	1/2	IIBR-100	NCT04608305	[105]
	Merck Sharp & Dohme/ IAVI	1	V590-001	NCT04569786	[105]
mRNA VACCINES	Curevac	1/2	CVnCoV	NCT04515147	[103]
	CureVac AG	1	CV7201 RNActive®	NCT02241135	[105]
	BioNTech/Fosun Pharma/Pfizer	3	BNT162b2 and BNT162b1	NCT04368728	[104-107]
	Moderna Therapeutics	1	mRNA-1325	NCT03014089	[105]
	Moderna Therapeutics	1	VAL-506440 (mRNA-1440)	NCT03076385	[105]
	Moderna Therapeutics	1	VAL-339851 (mRNA-1851)	NCT03345043	[105]
	Moderna Therapeutics	1	mRNA-1944	NCT03829384	[105]
	Moderna Therapeutics	1	VAL-181388 (mRNA-1388)	NCT03325075	[105]
	Moderna/NIAID	1/2	LNP-encapsulated mRNA	NCT04283461NCT04405076	[104]
	Moderna/NIAID	3	mRNA-1273	NCT04470427	[103, 106, 107]
SaRNA VACCINES	HDT Biocorp./University of Washington	N/A	LION/repRNA-CoV2S	doi: https://doi.org/10.1126/scitranslmed.abc9396	[103]
	Imperial College London	1	LNP-nCoVsaRNA	ISRCTN17072692	[103]
	Arcturus/Duke-NUS	2	ARCT-021	NCT04480957	[103]
	People's Liberation Army (PLA) Academy of Military Sciences/	1	ARCoV	ChiCTR2000034112	[105]

GENRE	ESTABLISHMENT	CLINIC PHASE	PROPER NAME	REGISTRY INDEX	REFERENCES
	Walvax Biotech.				
DNA VACCINES	Genexine Consortium	1/2	GX-19	NCT04445389	[103, 107]
	Cadila Healthcare Limited	1/2	nCov Vaccine	CTRI/2020/07/026352	[103]
	Osaka University/AnGes/Takara Bio	1/2	AG0301-COVID19 and AG0302-COVID19	NCT04463472NCT04527081	[103]
	Inovio Pharmaceuticals/International Vaccine Institute	1/2	INO-4800	NCT04447781	[103]
	Inovio Pharmaceuticals	1	INO-4700	NCT02670187	[105]
	Inovio Pharmaceuticals	1	INO-4201 and INO-4202	NCT02464670	[105]
	Imperial College London	1	GTU®- MultiHIV B	NCT02075983	[105]
	NIAID	1	VRC SARS	NCT0009946	[105]
	NIAID	1	VRCWNVD	NCT0030417	[105]
	NIAID	1	VRCFLUDNA057-00-VP	NCT00973895	[105]
	Osaka University/ AnGes/ Takara Bio	1/2	AG0301-COVID19	NCT04527081	[105]
	Cadila Healthcare Limited	1/2	ZyCoV-D	CTRI/2020/07/026352	[105]
	Genexine Consortium	1/2a	GX-19	NCT04445389	[105]
	Symvivo	1	bacTLR-Spike	NCT04334980	[105, 107]
	Providence Health and Services	1	CORVax12	NCT04627675	[105]
PROTEIN SUBUNITS	Kentucky Bioprocessing, Inc.	1/2	KBP-COVID-19 / KBP-201	NCT04473690	[103]
	FBRI SRC VB VECTOR, Rospotrebnadsor, Koltsovo	1/2	EpiVacCorona	NCT04527575	[103]
	Sanofi Pasteur/GSK	1/2	SARS-CoV-2 vaccine formulation 1/2	NCT04537208	[103]
	Anhui Zhigei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences	2	Recombinant new coronavirus vaccine (CHO cell)	NCT04466085	[103]
	Novavax	3	SARS-CoV-2 rS/Matrix-M1 Adjuvant (NVX-CoV2373)	2020–004123–16 NCT04533399	[103]

8. Conclusions

Scientists are working hard to determine the new coronavirus's characterization and develop antivirus therapies and vaccines. However, the virus's pathogenesis is still not fully known, and new studies are needed in this regard. Currently, the only way to prevent the spread of Covid-19 is an effective infection control method. The most appropriate treatment for patients under observation diagnosed with Covid-19 is still unknown. Therefore, treatment protocols should be followed within the framework of existing health rules. As a result, there are three main ways to end pandemics: (i) forming protective antibodies by encountering the disease of the majority of the society, (ii) reducing the disease-prone population by using a vaccine or preventive drugs, and (iii) reducing the infectiousness and pathogenicity (disease-causing) of the agent. There is no sign of 3rd way regarding the Covid-19 pandemic yet. The 2nd way some vaccines have been developed, and the prophylactic drug has not yet been

developed, although intensive trials are ongoing for both. There remains only the 1st way. But in that method, too, the death rate is very high. Turkey is one of the countries taking the earliest precautions in the world regarding COVID-19. In this context, Turkey: (i) for the source of the disease (finding the source, reporting the disease, definitive diagnosis, treatment of patients, isolation, search for carriers, surveillance of suspects, health education), (ii) for the infection way (correction of environmental conditions, control of food and beverages, health education, use of personal cleaning and protective equipment, restricting population movements) and (iii) oriented for healthy person safeguards (quarantine, observation) measures have been taken and continue to be taken. Although some vaccines have been developed for the COVID-19 coronavirus, intensive work is still being done to develop specific drugs or vaccines.

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Conflicts of Interest

The authors declare no conflict of interest.

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