Insights into SARS-CoV-2, its Variants and Therapeutic strategies for COVID-19 infection; a review

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ABSTRACT

Covid-19 is an infectious disease caused by the SARS-CoV-2. This virus has undergone mutations which has resulted in evolution of its several variants so far. The technical advisory group of World Health Organization (WHO) have declared all such SARS-CoV-2 variants (*alpha, beta, gamma delta, & lambda*) as variants of concern (VOC). These variants were quite challenging in terms of being fatal, hence, many therapeutic strategies were devised to restrict their infectibility. In this regard, multiple approaches were formulated by the scientists to possibly limit the spread of SARS-CoV-2. Our main concern in this study is also to analyze and summarize information regarding such strategies to treat COVID-19 infection. The mainly focused areas regarding this aspect in this study include traditional therapeutic practices, comprising vaccination and oral antiviral drugs. Moreover, some of the advanced breakthroughs in this area have also been discussed which include anti-inflammatory agents, corticosteroids and nanobody-like molecules.

Keywords: Antiviral agents, COVID-19 infection, SARS-CoV-2, Therapeutics, Vaccines.

1. INTRODUCTION TO SARS-CoV-2 & ITS VARIANTS

The global pandemic of novel coronavirus disease 2019 (COVID-19) produced by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was originated in Wuhan China and reported by World Health Organization (WHO) on 31st December 2019 (Sanders *et al.*, 2020). SARS-CoV-2 belongs to the largest group of viruses family that tends to specifically affect the human respiratory organs (Mandal, 2021). On April 5, 2020, there were more than 1.5 million reported cases with 69000 confirmed deaths in approximately 200 countries around the world.. Therefore, SARS-CoV-2 became the third zoonotic coronavirus that exhibited human-to-human transmission which also became the major cause of global pandemic (Fagni *et al.*, 2021).

The word "corona" means "crown," which refers to a spherical virus with peplomers, or crown/spike proteins, sticking out in all directions from the axis' center (Alinia-ahandani, 2020). The virus is crucial because it spreads quickly thanks to its positive sense single-stranded viral RNA genome. Bronchoalveolar lavage fluid and throat swabs from nine patients who visited the Wuhan seafood market during the initial outbreak were taken in order to study the characteristics of the coronavirus. The coronavirus was isolated using specialized human airway epithelial (HAE)

cells that are pathogen-free. After checking for cytopathic effects in HAE cells, more supernatant was collected for RT-PCR tests. It was discovered through phylogenetic research that bats may be the source of SARS-COV-2 (Kumar *et al.*, 2020; Chakraborty, Bhattacharya and Sharma, 2022). The host immunological response against SARS-CoV-2 is characterized as a chemokine storm and includes the overproduction of proinflammatory cytokines like interleukin (IL)-6, tumor necrosis factor (TNF), growth factors like granulocyte-macrophage colony-stimulating factor, and chemokines like IL-8 (Fagni *et al.*, 2021).

One of the important characteristics regarding SARS-CoV-2 to be studied was its morphology. In this regard, samples were collected from the nasopharyngeal and oropharyngeal tracts. The objective of these specimen collection was to explore the structural attributes of this virus using the transmission electron microscopy (TEM). After 3 days of processing, it was revealed that the virus had the largest RNA genome of almost 30kb in length where the particle size of the virus was ranging from 70 to 90 nm. TEM also showed a variety of intracellular organelles that were seen to be present in the virus (Yan *et al.*, 2020). Each component of the viral genome was enveloped into a helical nucleocapsid, surrounded by a lipid bilayer. The viral envelope was made up of 3 proteins that include membrane protein "M", the envelope protein "E", and the spike protein "S". The spike protein was found to be responsible for the pathogenicity of this virus (Kumar *et al.*, 2020). This S protein found to be the inducer of neutralizing antibodies (NABs) that are produced by the humoral immunity of our body. The mutations that occur in spike protein vary from variant to variant (Gobeil *et al.*, 2021). In the following composite figure, figure A demonstrates a general structure of coronavirus while, figure B, the three-dimensional structure of spike protein. The pattern of the following composite figure was taken from the findings of S. Kumar *et al*. (2020) (Kumar *et al.*, 2020).

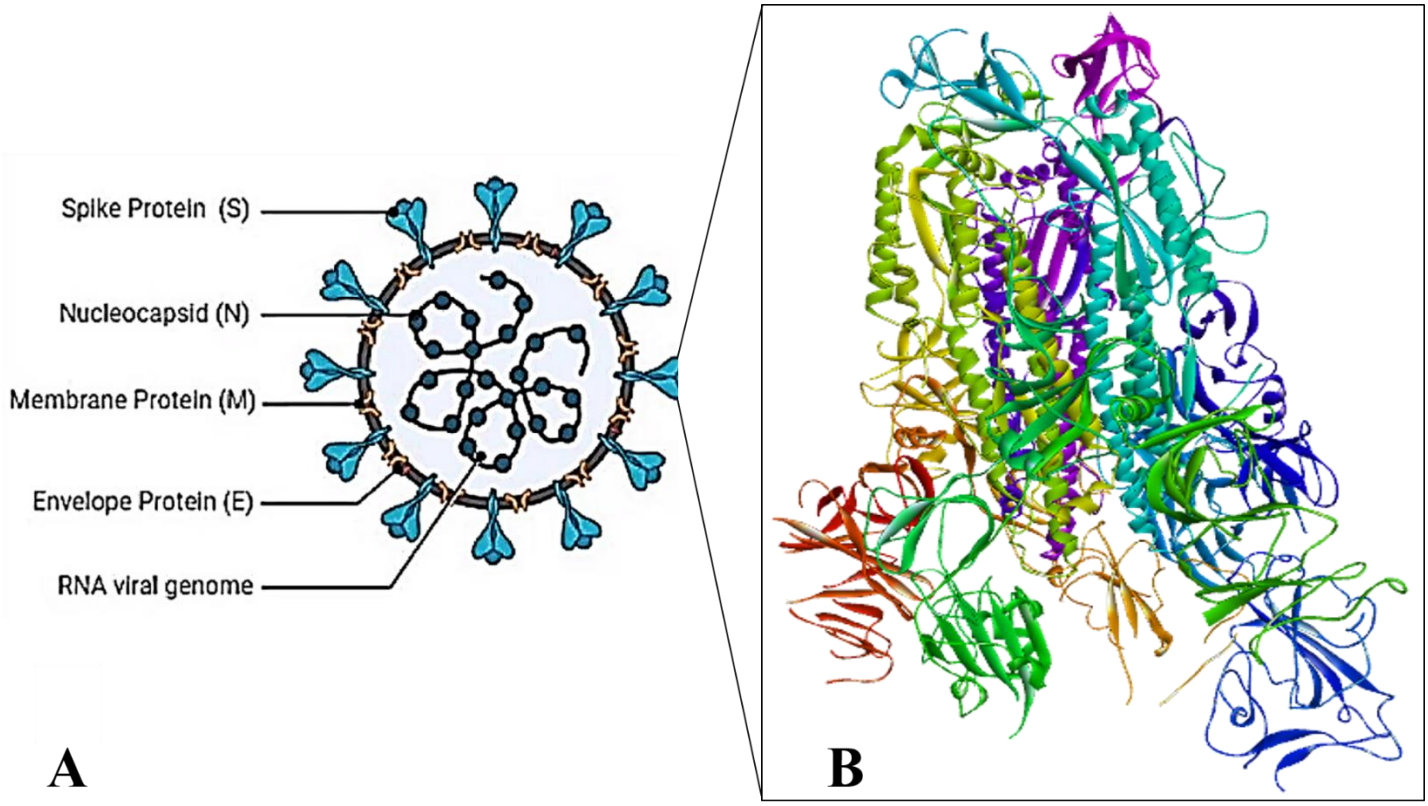

Figure 2. A: Demonstration of the basic structure of coronavirus; **B:** Three-dimensional (3D) structure of Spike protein of coronavirus

The above diagram of coronavirus (figure 2A) is designed by utilizing an online web-based tool named biorender (https://biorender.com/), while that of spike protein (figure 2B), the PDB file of it was downloaded from protein databank (PDB) (https://www.rcsb.org/structure/7FCD) whose accession number was 7FCD and its visualization was made by using Discovery Studio.

Regarding the variants of SARS-CoV-2, the studies have revealed that all of the variants represented the homology within the same family and possessed a positive-sense RNA strand genome (Hulswit, de Haan and Bosch, 2016). All such variants of coronavirus are subdivided into the genera, mentioned in table 1 (Burrell, Howard and Murphy, 2017; Li *et al.*, 2022a). World health organization has classified the coronavirus variants using Greek alphabets as have been shown in the table 1. Moreover, the table 2 is representing a comprehensive detail on SARS-CoV-2 variants, their respective regions of emergence, their respective common symptoms observed in patients, total number of mutations that were reported in every variant and the mutated sites in each of the variant.

Table 1. Names of coronavirus variants and their relevant host sources. The data in the following table was retrieved from the reported study of Li C *et al.* (2022) (Li *et al.*, 2022b)**.**

SARS-CoV-2 Variants	Sources (Host)
α (Alpha)	Human virus (HCoV-229E) and another not human coronavirus (HCoV-NL63)
β (Beta)	the prototype mouse hepatitis virus (MHV), including the human viruses HCoV-OC43, SARS-HCoV, and HCoV-HKU1
γ (Gamma)	viruses of cetaceans' birds and whales
λ (Lambda)	N/A
δ (Delta)	virus of pigs and birds
Omicron	N/A

Table 2. Summarized relevant details of SARS-CoV-2 variants. The data in the following table was collected from the studies reported by L. Van Blargan *et al.* (2022) and S. Kumar et al. (2022) (Fang and Shi, 2022; Kumar *et al.*, 2022)**.**

Name of variant	First outbreak	Symptoms	No. of Mutations	Mutated Sites
Alpha, (B.1.1.7)	The United Kingdom, (September 2020)	None Chills Loss of appetite Headaches Muscle aches	9	Del 69-70, del 144Y, N501Y, A570D, D614G, P681H, T7161, S982A, D1118H
Beta (B1.1351)	South Africa, (September 2020)	similar to alpha one's mild flu, body aches fever with loss of smell/taste	10	L18F, D80A, D215G, Del242-244, R2461, K417N, E484K, N501Y, D614G, A701V
Gamma, P.1 (B.1.1.28.1)	Japan/Brazil, (December 2020)	common cold, runny nose, body pain, and no other distinguishable symptoms are indicated	11	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T10271
Delta (B.1.617.2)	India, (December 2020)	Fever or chills, cough, Shortness of breath or difficulty breathing, Fatigue, Muscle or body aches, Headache, New loss of taste or smell, Sore throat, Congestion or runny nose, nausea or vomiting, Diarrhea,	7	RSYLTPGD246253N, G75V, T761, GT75-76V1, T859N, L452Q, F4905

Lambda, (C.37)	(Peru, June 2020)	Fever, cough, nasal congestion, fatigue, and muscle pain, diarrhea, headache, a respiratory infection.	15	T19R, T951, V70F, del156, A222V, W258L, G142D, del151, R158G, K417N, L452R, T478K, D614G, P681R, D950N
Omicron (B.1.1.529)	South Africa, (November 2021)	Asymptomatic infection, body ache, cough, fainting, fatigue, fever, headache, loss of smell or taste, nasal congestion, upper respiratory tract infection, skin rash, sneezing, and sore throat.	50	A67V, Δ69-70, T95I, G142D, Δ143-145, N211I, L212V, ins213-214RE, V215P, R216E, **G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R**, **G496S, Q498R, N501Y, Y505H**, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F

In context of discussing the SARS-CoV-2 variants it is also crucial to discuss all such mutants in terms of the resistance they show against certain antiviral drugs. In this regard, Paxlovid which is one of the prominent viral inhibitor was taken into account to unveil the resistant mutants. Nirmatrelvir is one of the active ingredients of Paxlovid hence, the resistance of SARS-Cov-2 was analyzed against this compound. Yanmei Hu *et al.* (2022) studied the M^{PRO} mutants in this respect and by sequence analysis found various mutations including T21I (B.1.1.318), L89F (B.1.2), G15S (C.37 Lambda), L205V (P.2 Zeta) and P132H (B.1.1.529 Omicron). All such mutations were found to lie outside the nirmatrelvir binding site on M^{PRO}. The mutants show reduced enzymatic activity and also resistance to nirmatrelvir (Ki > 10-fold increase) (Hu *et al.*, 2022).

2- THERAPEUTIC APPROACHES FOR SARS-COV-2

2.1 DIAGNOSIS

The pandemic was identified based on clinical symptoms. The crucial evidence for the diagnosis of the COVID-19 is a disclosure history or close associations with patients who are either suspected or approved. However, clinical characteristics and imaging appearances can suggest possible Covid-19 in patients with an unknown medical history. Real-time reverse transcription polymerase chain reaction (RT-PCR) testing should be performed in such circumstances as a reference standard after the indication of suspected COVID-19 (Abbasi-oshaghi *et al.*, 2020). In order to diagnose a confirmed case, one should start with a suspected case and any one piece of pathogenic evidence, such as:

1 SARS-CoV-2 real-time PCR test was positive.
2 Viral whole genome sequencing, which is a quick and effective tool for studying viral

replication and host cell metabolism, demonstrates remarkable homogeneity to the known novel coronavirus.

3 Positive for the specific IgM and IgG antibodies to the SARS-CoV-2 in serum tests; or a change from a negative to a positive IgG antibody to the SARS-CoV-2; or an increase in titer of at least four times in the recovery phase over the acute period (Y. Y. Wang *et al.*, 2020).

The positive RT-PCR or the gene sequencing results should be used to confirm the final etiology diagnosis of COVID-19. For the prevention and management of this pandemic, the preliminary COVID-19 diagnosis is essential. The doctors should always be on the lookout for individuals with COVID-19 infection, who may have little or no clinical signs, a normal chest CT scan, or even an initial PR-PCT test result that is negative (Joseph, 2006). The steps for covid-19 test are explained in the following figure:

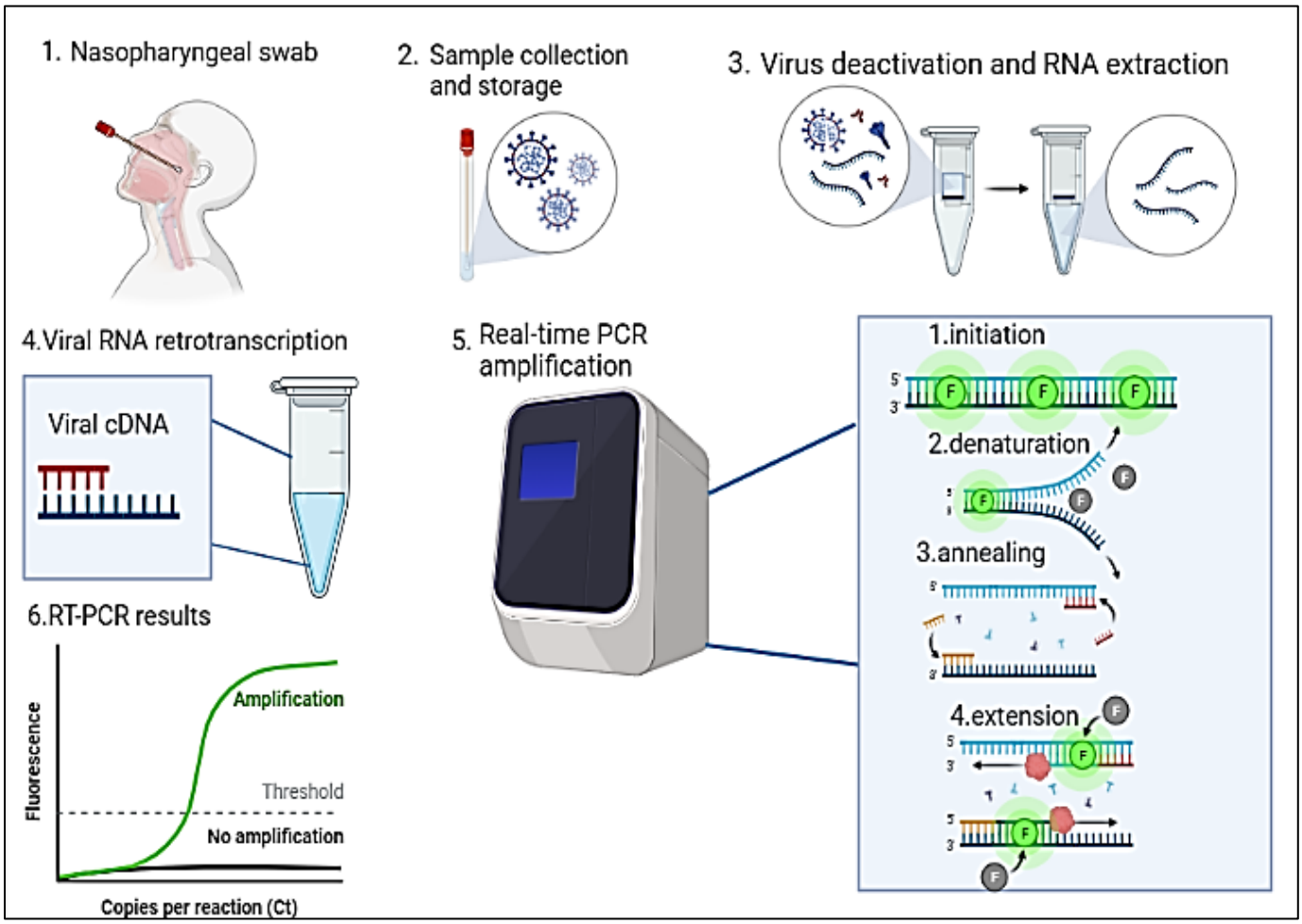

Figure 2. The step-wise graphical demonstration of COVID-19 diagnostic procedure, particularly by using PCR. The figure was made in an online tool i.e., Biorender (https://biorender.com/).

2.2 IMMUNOTHERAPY APPROACHES FOR COVID-19

2.2.1 VACCINES

To combat such a hazardous virus and assist the immune response in human body, different vaccines have been developed through various approaches. Vaccine candidates act as a precursor in the pipeline for the prevention of COVID-19. The inactivated (killed) or live attenuated nucleic acid, the recombinant subunits and the adenovirus-based vector vaccines have been made to prevent and treat the SARS-CoV-2 infection (Hadi, Khudhair and Al-Qaim, 2021). The inactivated viruses are non-infectious and may show identification with other viral proteins to the immune system and have a stable expression of the antigenic epitope for inflammatory response (Fiolet *et al.*, 2022). This method has been used in the past to prevent the diseases such as influenza. (Fagni *et al.*, 2021). PiCoVacc is a vaccine containing inactivated virus (SARS-CoV-2) which stimulated the release of antibodies in rhesus macaques, mice, rodents but there was no detectable change in the level of cytokines in the rhesus (Yan *et al.*, 2020). Therefore, vaccines containing nucleic acids consisting of RNA, DNA encoding antigen or mRNA to induce immunity either (humoral or cell-mediated) in the host were taken into consideration and even proceeded to the clinical trials of phase III. Nucleic acid-containing vaccines can be manipulated and processed to generate immunity but they also have certain drawbacks (Hadi, Khudhair and Al-Qaim, 2021). Following figure demonstrates the development of various types' vaccines and the release of antibodies as resulted immune response, generated.

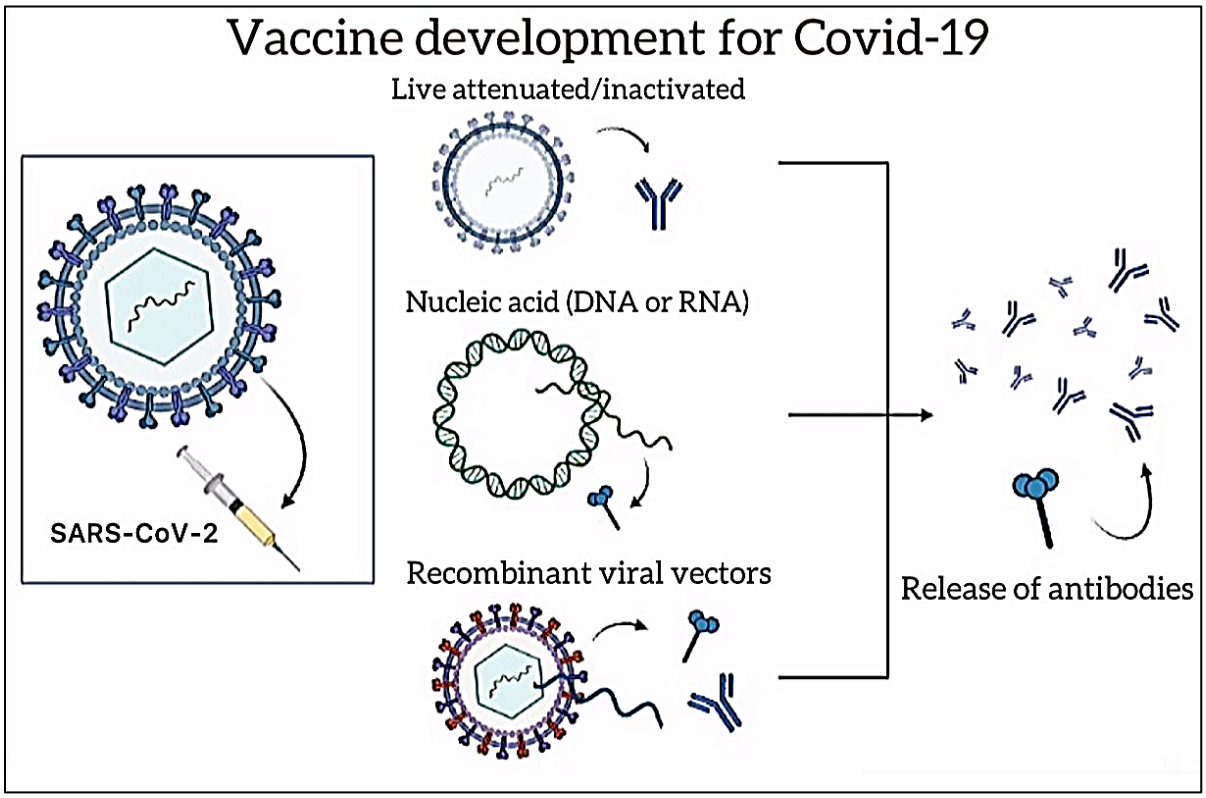

Figure 3. Demonstration of Vaccine development and antibodies release. The format of this mechanism-based vaccines is gathered from the findings of P. Bhattacharyya *et al.* (2021) and drawn in Biorender (https://biorender.com/) (Pollet, Chen and Strych, 2021)**.**

Multiple vaccines candidates have been developed regarding SARS-CoV-2 so far, by utilizing different approaches. Some of such vaccines which were widely administered worldwide to inhibit COVID-19 have been discussed below in table 3. The details regarding the approaches followed to develop respective vaccines and their efficacies in percentages have also been comprehensively summarized in the following table.

Table 3. Table representing multiple vaccines along important details. The summarized data in the above table is derived from the reported studies by Pollet *et al.* (2021) and T. Fiolet *et al.* (2022) (Pollet, Chen and Strych, 2021; Fiolet *et al.*, 2022)**.**

Vaccine	Technology used	Clinical Trial regime	Efficacy after full administration of vaccines	Effective for genotypes at the time of trial
Viral Vector Based Vaccines				
Oxford-AstraZeneca **(AZD1222)**	Viral vector	**1 + 1 doses** (6-12 weeks apart)	81%	B.1.1.7, B.1.351, P.1, B.1.427/B.1.429, P.2, B.1.526 and C.37
Gamaleya **(Sputnik V)**	Viral vector	**1+1 dose** (21 days apart)	91.4%	No variants had been originated at the time of trials
Johnson & Johnson **(Ad26.COV2-S)**	Viral vector	1 dose	85%	B.1.351, P.1, B.1.427/B.1.429, P.2, B.1.526 and C.37
Inactivated Viral Vaccines				
Sinovac Biotech **(CoronaVac)**	Inactivated virus	**1 + 1 doses** (14 days apart or 28 days apart in Chile)	79%	P.1 and P.2
Sinopharm **(BBIBP-CorV)**	Inactivated virus	**1 + 1 doses** (21 days apart)	79.87%	No variants had been originated at the time of trial

mRNA Based Vaccines				
Pfizer-BioNTech (**BNT162b2**)	mRNA	1 + 1 (21 days apart)	92.1%	B.1.351, P.1, B.1.427/B.1.419, P.2 and B.1.526
Moderna **(mRNA-1273)**	mRNA	**1 + 1 doses** (28 days apart)	94.1%	B.1.427/B.1.429 and B.1.526
Protein Based Vaccines				
Novavax **(NVX-CoVC2373)**	Protein-based	**1 + 1 doses** (21 days apart)	Approx. 96.4%	B.1.1.7, B.1.351, B.1.427/B.1.429 B.1.526

2.2.2 ORAL AND INJECTABLE DRUGS

Molnupiravir is converted into Molnupiravir triphosphate inside the host cell body (Imran *et al.*, 2021). The replication of the RNA-dependent RNA-Polymerase (RdRp) enzyme present in virus is inhibited by the Molnupiravir triphosphate as it is incorporated in the RNA instead of nucleoside cytidine which results in mutation (A. K. Singh *et al.*, 2021). With the help of this mechanism, the virus could not replicate or do not take the control of host cell's replicating apparatus which will lead to the reduction in the severity of the disease (Sanders *et al.*, 2020). Under the phase II of clinical trials, the administrated dosage is randomized 1:1 to 200 mg molnupiravir or placebo, or 3:1 to molnupiravir (400 or 800 mg) or placebo, twice-daily for 5 days. The advantage of Molnupiravir is that it is an oral tablet that can be taken more conveniently as compared to the other clinical procedures (Fischer *et al.*, 2021). It has reduced the risk of hospitalization by about 50% but the cost is around $700 per person for a 5-day course. Hence, currently, the limitation of this drug is its cost but on the other hand, it has been proved to be effective too (Mahase, 2021; Pourkarim, Pourtaghi-Anvarian and Rezaee, 2022).

The rapid advancement of potent anti-SARS-CoV-2 vaccines has been a successful countermeasure to lower hospitalisation and mortality rates in many nations. In this regard, ritonavir, a strong CYP3A4 inhibitor that slows nirmatrelvir metabolism, was also given in combination with nirmatrelvir, an orally bioavailable Mpro inhibitor, to treat SARS-CoV-2 patients (Joyce, Hu and Wang, 2022). However, an Antiretroviral medication is also used traditionally to treat HIV (Gardner *et al.*, 2009). Its treatment disrupts the replication of SARS-CoV-2 in the body by binding to 3CL- like protease (Lamb, 2022), which is crucial for the function and replication of the virus (Gobeil *et al.*, 2021). The typical regimen of dosage is 400 mg/100 mg orally twice per day or (400/100 mg)/5 mL oral solution for 14-day time period. Higher doses are avoided due to severe gastrointestinal tract infections.

The scheduled interim analysis has shown that people with Ritonavir (if authorized) to use at home will have reduced 89% of the risk of severity of COVID-19 infection in patients (Jomah,

Asdaq and Al-Yamani, 2020). Moreover, it will further prevent the transmissibility of viruses. Surprisingly, the novel antiviral candidate has been proved to be effective against multiple antiviral infections as reported by Pfizer. Similarly, to analyze the efficacy of Paxlovid in treating the SARS-CoV-2 patients, a clinical trails based study was carried out in which 180351 patients were incorporated. Paxlovid was administered in 2.6% of the total number of patients while, 75.1% were subjected to vaccination. The results suggested that Paxlovid was found to be quite effective in curing even the immunocompromised patients including those who were already suffered from cardiovascular and neurological diseases (Najjar-debbiny *et al.*, 2022).

In the previous discussion in this particular section, oral medications have been discussed. Let's have insights into some of the potential intravenous (I.V) antiviral drugs. *Remdesivir* is one of these I.V drugs, administrated intravenously after reacting with an enzyme, considered as a treatment of Covid-19 (Sanders *et al.*, 2020). It is a broad-spectrum antiviral drug and has considerable efficacy against RNA viruses. Studies have shown that RDV had been proved as a chain terminator in Ebola virus and MERS-CoV. But this drug has high genetic hurdle against resistance in coronaviruses so multiple doses are administrated (Hendaus, 2021). This drug contains an active compound (GS-441524) that inhibits the viral polymerase protein from being translated and in this way the increase in viral copy number decreases (Hashemian *et al.*, 2022). The intravenous dosage is 200 mg as a single dose on day 1, followed by 100 mg once daily and duration is generally 5 days and efficacy are 76% after complete course. It has reduced 87% hospitalization. Depending on its efficacy it has been approved by FDA as well as by WHO and has been proved to be effective against covid-19 variants also (Grein *et al.*, 2020). Following figure generally demonstrates the mechanism of action of all such medications.

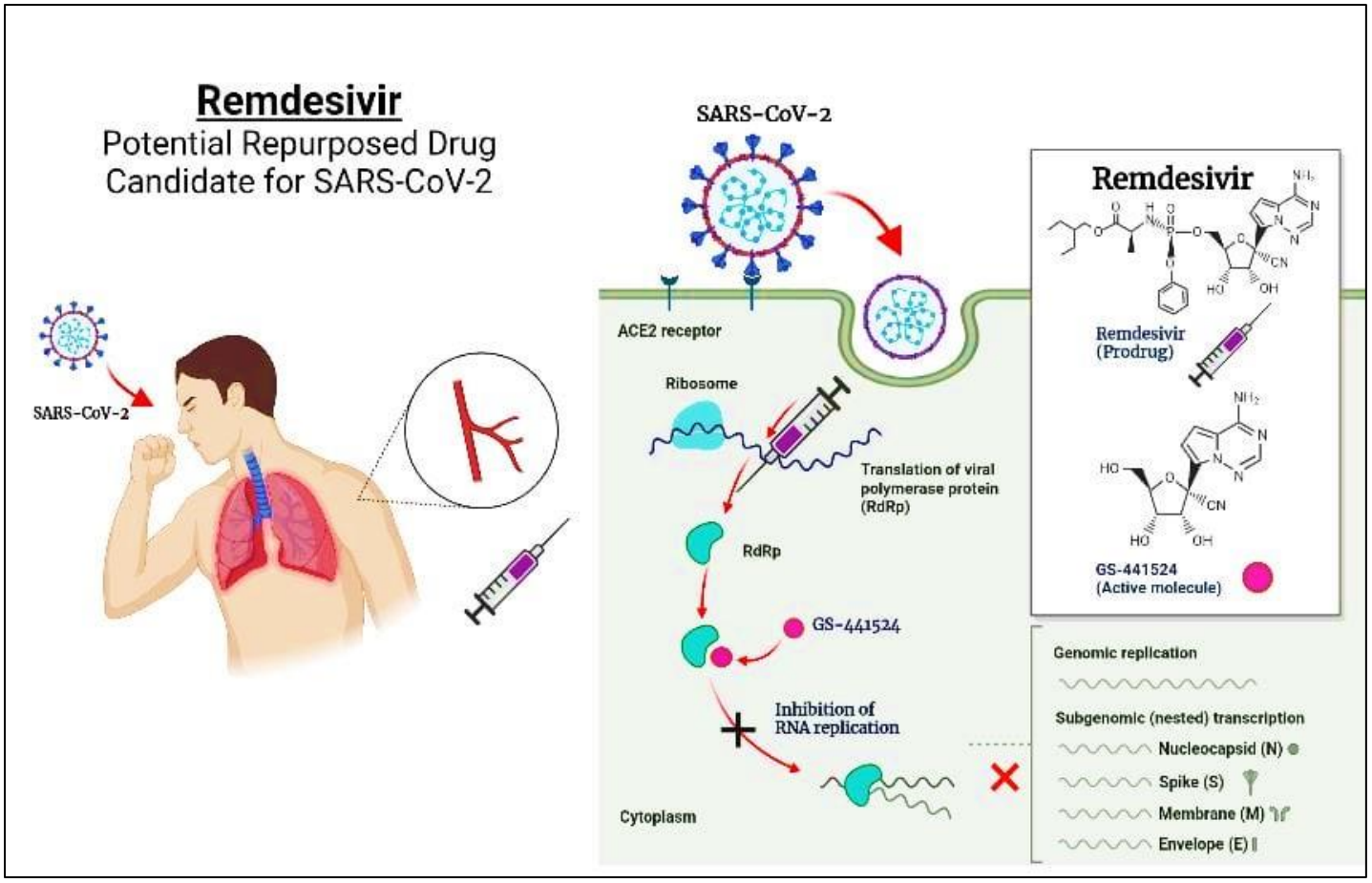

Figure 4. Mechanism of action of Corona Pills. The format of above illustrated figure is adopted from the respective articles of L. Zhang and R.Zhou (2020) and A. Saha *et al.* (2020) and drawn in Biorender (https://biorender.com/) (Saha *et al.*, 2020; Li *et al.*, 2022b)**.**

The following table comprehensively summarizes all the details which also encompass the effectiveness and non-effectiveness regarding various antiviral drugs that have been discussed as potent medications for COVID-19 infection.

Table 4. Important descriptions of COVID-19 Medications. The data gathered in following table is retrieved from various findings that have been made in order to elucidate important parameters of different antiviral drugs (Cao *et al.*, no date; A, 2020; Ma *et al.*, 2022).

Antiviral drugs	Doses	Efficacy	Mechanism	Clinical trial	Reduced Hospitalizations
Oral Drugs					
Molnupiravir	randomized 1:1 to 200 mg molnupiravir	Participants receiving 800 mg molnupiravir	Molnupiravir is converted into Molnupiravir	Phase II clinical trials has shown accelerated	Reduced hospitalization by 50%

	or placebo, or 3:1 to molnupiravir (400 or 800 mg) or placebo, twice-daily for 5 days	(1.9%) versus placebo (16.7%), time was decreased for patients with 800 mg of molnupiravir.	triphosphate. The replication of RNA-dependent RNA-Polymerase (RdRp) enzyme in virus is inhibited. As it is incorporated in the RNA instead of nucleoside cytidine which results in mutation.	SARS-CoV-2 RNA clearance and elimination of infectious virus.	
Lopinavir-Ritonavir	N/A	Non-effective	Lopinavir-Ritonavir did not show inhibition activity against SARS-CoV-2 M^{PRO} hence, it is a weak inhibitor	In initial trials, the administration of lopinavir-ritonavir in patients was terminated due to adverse effects	N/A
Intravenous Drugs					
Remdesivir	IV: 200 mg as a single dose on day 1, followed by 100 mg once daily. Duration is generally 5 days	IV: 200 mg of Remdesivir has efficacy of 76% after complete course of 5 days.	drug contains an active compound (GS-441524) that inhibits the RdRp protein from translation, viral multiplication decreases	Early phase 1 clinical trials	Reduced hospitalization by 87% after the completion of 5-day course.

2.2.3 ADVANCED APPROACHES TO LIMIT SARS-CoV-2 PATHOGENICITY

At the start of the pandemic, chloroquine and hydroxychloroquine were frequently utilized. Due to their various pharmacological features, they appeared to be viable medications for the treatment of COVID-19 (Zanza *et al.*, 2022). They increase the production of other inflammatory mediators while inhibiting the synthesis of cytokines like IL-1 and IL-6 (Savarino *et al.*, 2020). As a result, the anti-inflammatory properties of chloroquine and hydroxychloroquine are present. They additionally shown antiviral efficacy against a variety of bacteria, including SARS-CoV-1. Their defensive efficacy against SARS-CoV-2 infection appeared to be confirmed by preliminary in vitro and in vivo results (Gao, Tian and Yang, 2020; M. Wang *et al.*, 2020).

Some of the findings in this context have also shown that they have little to no effect on COVID-19 prevention or therapy. Additionally, they were linked to a higher chance of negative outcomes (B. Singh *et al.*, 2021). Thomas M Drake *et al.* (2021) have reported that non-steroidal anti-inflammatory drugs (NSAIDs) are not linked to worse COVID-19 outcomes (Drake *et al.*, 2021). Moreover, another study have also reported that Baricitinib, ruxolitinib, and eculizumab are among the medications that being evaluated in COVID-19 patients which can lessen hyperinflammation (Scavone *et al.*, 2022).

Given that oral dexamethasone has demonstrated efficacy, therapy with inhaled corticosteroids (ICS) may also be successful in COVID-19 (Robinson *et al.*, 2022). Corticosteroid is quickly delivered by ICS directly to the lungs, where it may reduce ACE2 expression and subsequently SARS-CoV-2 entry into the cells (Finney *et al.*, 2020). Early studies point to budesonide inhalation as beneficial in early COVID-19 (Ramakrishnan *et al.*, 2020; Yu *et al.*, 2021). Inhaled corticosteroids at recognized doses have negligible systemic effects (Christensson and Thor, 2008). Philip C. Robinson *et al.* (2022) have reported that the IFN, a class of proteins with strong antiviral activity, offers a different inhaled alternative. The severity of COVID-19 is significantly reliant on the endogenous level of type 1 IFN, according to studies evaluating genetic predisposition to severe infection and naturally occurring autoantibodies against IFN. ('Inborn errors of type I IFN immunity in patients with life-threatening COVID-19', 2020; 'Autoantibodies against type I IFNs in patients with life-threatening COVID-19', 2020; Robinson *et al.*, 2022).

E.M. Obeng, C.K.O. Dzuvor, and M.K. Danquah (2022) reported a significant breakthrough in this context of the recently mentioned methodologies. The primary area of interest in this study was the usage of nanobody-like compounds and nanobodies. The heavy chain-only antibodies (HCAbs) from alpaca, llama, and dromedary are the source of the single-domain, antigen-specific fragments known as nanobodies (Hamers-Casterman *et al.*, 1993). The interactions between nanobodies and the coronavirus spike protein can be divided into three main categories: receptor binding site (RBS), non-receptor binding site (nRBS), and overlapping cahoot interactions. The nanobody for the RBS category preferentially binds to the ACE2 receptor-associated epitope on the spike RBD in the absence of ACE2, causing the fusion machinery to be activated before it is ready. Though it might not alter the RBD architecture, this decoy contact does stop virus entry and cell membrane fusion. The nRBS class, on the other hand, interacts with the spike protein's other components to change its conformational choice and render it incapable of

interacting with cell membranes. Finally, in the overlapping cahoot, which is positioned between RBS and nRBS, the nanobody-spike protein interaction occurs at the intersection of the two scenarios mentioned before. Inhibition and distortion of conformational validations are the outcomes in this case (Obeng, Dzuvor and Danquah, 2022).

S. Bhowmick *et al.* (2021) highlighted another novel approach regarding the inhibition of COVID-19 infection in their respective reported study. In-silico modeling and simulation platform was employed in this context and four such food related compounds were figured out that were found to suppress the papain-like protease (PLpro) of SARS-CoV-2. This food-PLpro complex was found out to be a potential inhibition interaction. Another important compound i.e., GRL0617 was also found to be an effective PLpro inhibitor. GRL0617 (4) has emerged as a leading candidate as the SARSCoV-2 PLpro inhibitor due to the fact that the SARS-CoV-2 PLpro is 83% identical to and 90% similar to the SARSCoV PLpro. There have been encouraging developments in the development of GRL0617 analogues into powerful SARS-CoV-2 PLpro inhibitors since the start of the COVID-19 pandemic. However, GRL0617 (4)'s moderate to insignificant antiviral activity prevents it from moving forward to animal model studies (Tan *et al.*, 2022). Furthermore, direct comparisons to the known standard inhibitor and the proposed food compounds both point to the possibility of these substances acting as active chemical modifiers of the SARS CoV-2 PLpro protein's function (Bhowmick *et al.*, 2022).

H.J.T. Coelingh Bennink *et al.* (2022) have reported a never applied but an efficient method to inhibit the SARS-CoV-2 entry into the cells. Various effects of human sex hormones in both males and females were studied in this study i.e., estrogen and testosterone. It was concluded that there were specific host-cellular proteins that promote viral entrance in cells include, TMPRSS2 and ACE2. Both testosterone and oestrogen levels can be increased or decreased to suppress both proteins. Therefore, COVID-19 viral cell entrance may be reduced by both androgen-deprivation therapy (ADT) and oestrogen therapy (ET). It was also considered that ADT and ET in combination (ADET) has never been investigated as a potential treatment for SARS-CoV-2. Thus, it was hypothesized that ADET would be an efficient and safe treatment for SARS-CoV-2, to be proven in a clinical trial, based on the mode of action of the combination (Coelingh Bennink, Egberts and Debruyne, 2022).

3- CONCLUSION

All the discussion addressed in this study is based on COVID-19 pandemic and real-time analysis. Due to emerging variants of coronavirus and their mutating nature, it has become a challenging task for the scientists to limit their infection. World Health Organization (WHO) is expecting more recombinants having more transmissibility and mutations in spike glycoproteins. Various vaccines have been developed so far, to induce antibodies and boost up the immune system to tackle such variants. Scientists are working to devise more advanced therapeutic strategies as well, in this regard. One of such recent breakthroughs are Corona Pills (*both oral & I.V drugs*), that have been developed as a source of medication especially for omicron variant. Many investigations and experimentations are still underway to make such broad spectrum vaccines and

antiviral drugs to tackle the upcoming variants of coronavirus. In addition to these mentioned approaches, more drugs may be introduced against COVID-19 in near future. The vaccines may be able to tackle the parent pathogen but the mutated variants might not be possible to be controlled by just vaccines in near future. That is why it is of great concern to adopt other advanced approaches in this context. Keeping in view this point of fact, the efficacy of several combinations of antiviral drugs have also been tested against SARS-CoV-2 infection. Since, mutated variants possessed increased forms of antiviral drugs resistance, therefore, to augment the effect the antiviral drugs were then administered in combined form. For example, Pibrentasvir and Ombitasvir serve as inhibitors of SARS-CoV-2 exonuclease inhibitors, hence they were introduced along other active prodrugs such as Molnupiravir, Sofosbuvir and Remdesivir to inhibit the effect of exonuclease against them. As have been discussed earlier, many anti-inflammatory drugs and corticosteroids can also be incorporated. Nanobodies based approach was also found to be one of the appealing and reliable source of COVID-19 therapy in patients. Lastly, by suppressing the androgens and elevating the estrogen levels in the body has also been hypothesized to possibly inhibit the SARS-CoV-2 entrance inside the host cell to ultimately inhibit this virus-mediated infection.

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