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Review

# Navigating the COVID-19 Therapeutic Landscape: Unveiling Novel Perspectives on FDA-Approved Medications, Vaccination Targets, and Emerging Novel Strategies

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**Abstract:** Amidst the ongoing global challenge of the SARS-CoV-2 pandemic, the quest for effective antiviral medications remains paramount. This comprehensive review delves into the dynamic landscape of FDA-approved medications repurposed for COVID-19, categorized as antiviral and non-antiviral agents. Our focus extends beyond conventional narratives, encompassing vaccination targets, repurposing efficacy, clinical studies, innovative treatment modalities, and future outlooks. Unveiling the genomic intricacies of SARS-CoV-2 variants, including the WHO-designated Omicron variant, we explore diverse antiviral categories such as Fusion inhibitors, Protease inhibitors, Transcription inhibitors, Neuraminidase inhibitors, Nucleoside reverse transcriptase, and non-antiviral interventions like Importin  $\alpha/\beta 1$ -mediated nuclear import inhibitors, Neutralizing antibodies and convalescent plasma. Notably, Molnupiravir emerges as a pivotal player, now licensed in the UK. This review offers a fresh perspective on the historical evolution of COVID-19 therapeutics, from repurposing endeavors to the latest developments in oral anti-SARS-CoV-2 treatments, ushering in a new era of hope in the battle against the pandemic.

**Keywords:** Molnupiravir; SARS-CoV-2; drug repurposing; vaccines; variant of concerns (VOC); Paxlovid

## 1. Introduction

Coronaviruses (CoVs) are enveloped RNA viruses and are members of the order Nidovirales' Coronaviridae family that cause respiratory, hepatic, neurological, and intestinal disease. [1] Four endemic coronaviruses in humans, known as CoV-229E, CoV-OC43, CoV-NL63, and CoV-HKU1, are frequently linked to mild respiratory illness in healthy people. [2] Coronaviruses, such as the Middle East Respiratory Syndrome (MERS-CoVs), Severe Acute Respiratory Syndrome (SARS-CoV), [3] and, eventually, the new Severe Acute Respiratory Syndrome (SARS-CoV-2) that cause COVID-19, are all examples of deadly outbreaks caused by coronaviruses. [4-8] COVID-19 was proposed to be detected in SARS-CoV-2 in Wuhan, China, by December 2019. [3,4,9-12] As a result, the World Health Organization (WHO) directed various tests about the recent onset of this outbreak. [12,13] The outbreak, which was caused by COVID-19's initial appearance, came from an unidentified animal source at market, [12] but evidence suggested that zoonotic species, [14] including intermediate hosts

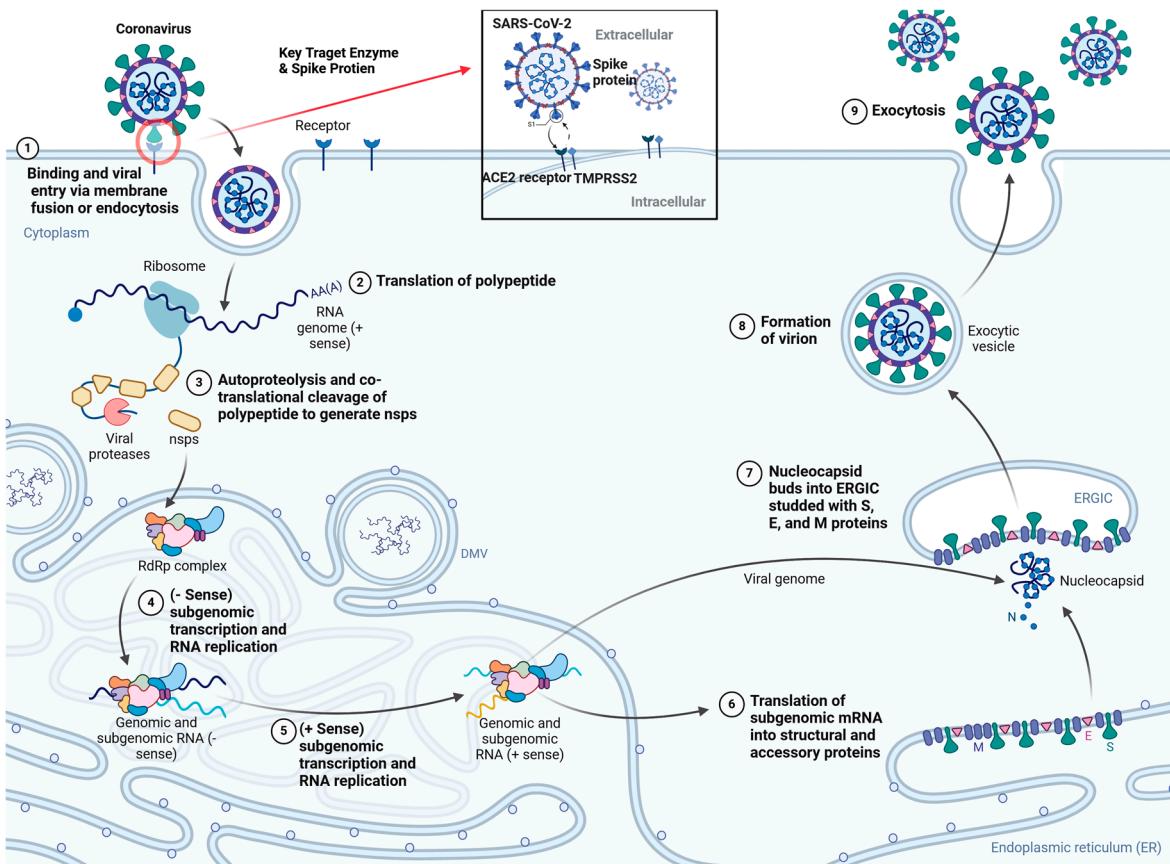
such as bats, were the main source of the infection. [10] SARS-CoV-2 is a positive single-RNA stranded virus that has the potential to infect humans or animals. SARS-CoV-2 belongs to the betacoronavirus subfamily, one of the four CoV subfamilies; gamma, delta, alpha, and beta. The beta and alpha CoV viruses attack mammals, but the delta and gamma COV viruses only affect birds. [8,15,16] SARS-CoV-2 exhibits persistent transmission from person to person via direct/indirect contact and through the environment as respiratory droplets and/or aerosols. [17–19] The research on SARS-CoV-2 suggests that the majority of cases could be caused by relatively low viral loads, with different symptoms ranging and lasting a variety of times. [20] The onset of more severe virus symptoms with a larger load can be seen in common symptoms such as fever and cough. [3,14] Some symptoms, including fever, inflammatory reactions, pneumonia, and hypoxemia, may manifest as the illness worsens. Most COVID-19 patients either show no symptoms or have mild illness, and respiratory patients should therefore visit hospitals. [5,20–22] Since December 2019, COVID-19 has been a significant public concern around the globe. On November 9th, 2021, over 250 million of COVID-19 patients were reported in 224 countries and territories. [23] The discovery of this novel virus has inspired researchers to create new vaccinations and test them to ensure their efficiency. [24] It is crucial to draw attention to the SARS-CoV-2 variations discovered in the genomes of SARS-CoV-2 virions. These variations are anticipated to have an advantageous effect on the phenotype of the virus in some circumstances. Such modifications may have an impact on the pathogenicity, transmissibility, infectiousness, as well as antigenicity of viruses. [25] On November 24, 2021, the World Health Organization classified the SARS-CoV-2 Omicron variant B.1.1.529, which appeared in South Africa, as a variation under monitoring (VUM). Two days later, the Omicron version was classified as a variant of concern (VOC). This variant has several mutations, with about 15 changes to the spike receptor-binding domain (RBD). [26]

There have been various proposed techniques to combat SARS-CoV-2. Among these, targeting ACE2 either directly through supplements or inadvertently through medications. [27] Additionally, the main protease (Mpro) has also been targeted to combat SARS-CoV-2. [7,28] Based on the preceding, it is crucial to gather and comprehend the earlier articles written about the attempts and trials made to resist COVID-19. [29,30] This article evaluates the majority of previously repurposed FDA-approved medications, their clinical studies, and the most recent possibilities for fighting SARS-CoV-2. This article could help researchers from around the globe in developing a comprehensive understanding of this pandemic and potential therapeutical approaches.

## 2. SARS-CoV-2 Structure, Life Cycle and Mechanism of Action

In the replication cycle of SARS-CoV-2 (Figure 1), the virus enters the host cell either through the fusion of its viral envelope with the host cell membrane or via an endosomal route. To initiate viral entry, the receptor-binding domain (RBD) of the spike (S) protein binds to the human host cell receptor (ACE2). [31,32] Subsequent to the RBD interaction with the receptor, the S protein undergoes proteolytic cleavage, facilitated by various host proteases such as TMPRSS2, furin, and cathepsin B/L. Following entry, SARS-CoV-2 releases its genomic RNA into the cytoplasm, utilizing both host cell and intrinsic enzymatic machinery to replicate its genetic material and form new viral particles.

The viral RNA genome is initially translated into viral replicase polyproteins (pp1a and pp1ab), which are then cleaved into 16 non-structural proteins (nsps). [33] In the genome replication and transcription process, mediated by the replication transcription complex (RTC), negative-sense (-sense) genomic RNA is synthesized. This RNA serves as a template for generating positive-sense (+sense) genomic RNA and subgenomic RNAs. The interaction of the viral genomic RNA with structural proteins located in the endoplasmic reticulum (ER) and ER-Golgi intermediate compartment facilitates viral formation (ERGIC). Eventually, these virions are exocytotically secreted from the infected cell and discharged to the plasma membrane through deacidified lysosomes.



**Figure 1.** Human Structure, life cycle, mechanism of action of COVID-19. Created with Biorender.

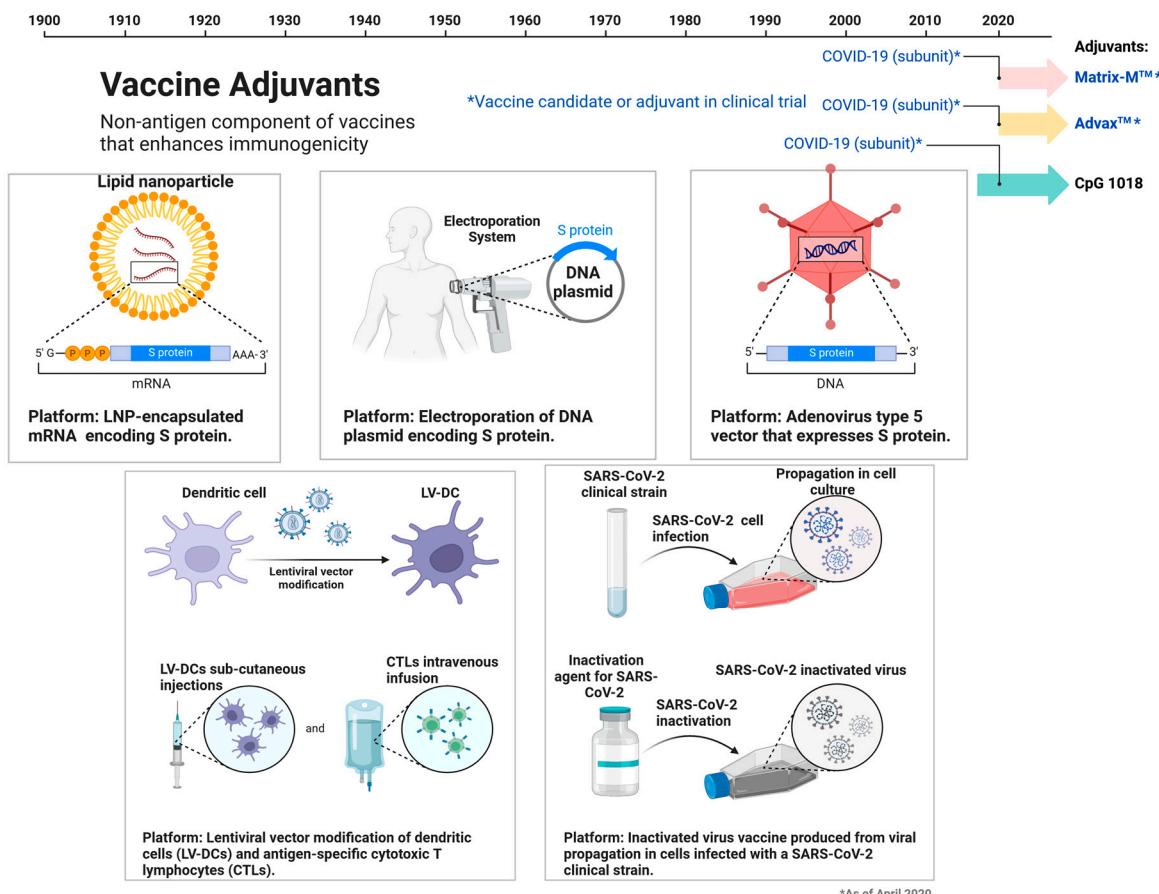
The human structure of COVID-19 consists of the innermost layer of SARS-CoV-2 and nucleocapsid (N) protein, which makes up the viral genome. As previously mentioned, SARS-CoV-2 is an RNA-positive virus that uses a ribosomal host to translate its genome as soon as it enters the cell. There are 29 different proteins encoded in the genome as a result. The envelope (E) protein is present in the nucleocapsid, while the membrane (M) protein is present across the entire virus envelope. In addition, the virus uses the spike (S) protein in the enclosed membrane on its surface when attached to host cells. Additionally, oesophageal cells, alveolar cells, cardiac cells, proximal kidney cells, and absorbent enterocytes exhibit angiotensin-converting enzyme-2 (ACE2) receptors as the other cell types do. [34] As a result, the (S) protein primes transmembrane serine protease 2 (TMPRSS2), prevents SARS-CoV-2 infection in lung cells. In TMPRSS2-negative cells, [35] the cysteine proteases cathepsin B/L can facilitate the cleavage of the S-protein. There are 7 non-structural proteins; (ORF)7a, PLpro, Nsp12, Nsp3c, Mpro, Nsp1, and Nsp13, and 4 structural proteins that SARS-CoV-2 encodes; M, S, N, and E. [36] A crucial goal for the development of novel antiviral drugs is the understanding of the fundamental components and biochemical mechanisms involved in the coronavirus replication cycle, including RNA-dependent RNA polymerases and proteolytic enzymes. Respiratory droplets mostly spread [37] SARS-CoV-2 in people, but it has also the potential to spread into the air. [38] The virus enters the host cells either by the endosomes or through plasma membrane. It interacts with ACE2 as an entry sensor, and the viral S protein, which facilitates attachment to the host cell membrane through both pathways. [35,39] According to a recent study, the host protease TMPRSS2 activates the connection between the S protein and the ACE2 protein. In order to easily connect to the host receptors, the virus employs the S protein to deactivate antibodies. [40] Beta coronaviruses typically employ hemagglutinin esterase (HE) to bind to sialic acid present on the glycoprotein surface, although the exact fusion mechanism of SARS-CoV-2 is not fully understood. To impede these fusion stages. [41] fusion inhibitors can be employed. Following the completion of fusion, the envelope is shed, allowing the SARS-CoV-2 genome, along with its nucleocapsid, to enter the host cell's cytoplasm. [35] Within its genome are open reading frames

ORF1a and ORF1b genes, generating two polyproteins (pp), pp1a and pp1b. These polyproteins, assisted by host ribosomes. [42] play a role in viral translation. Subsequently, papain-like protease (Ppro) and Mpro cleave the polyproteins, yielding various non-structural proteins. Based on a three-dimensional analytical model, it is suggested that, in addition to Ppro and Mpro, the presence of the 3C-like cysteine protease (3CLPro) in SARS-CoV-2 is likely, given its similarity to SARS-CoV, approximately 96%. [43] These proteases perform critical roles in transcription and replication of viruses. Furthermore, protease inhibitors that block these proteases have the potential to be antivirals against SARS-CoV-2. [44] The replication mechanism of SARS-CoV-2 based on models of MERS-CoV and SARS-CoV due to the similarity of their non-structural and structural proteins. RNA-dependent RNA polymerases are transcription and replication complexes formed by a non-structural protein known as nsp12 (RdRp). [45] In SARS-CoV, Nsp12 is coupled with its cofactors; nsp7 and nsp8. Using the initial positive RNA as a guide, this protein complex produces a complementary RNA with the opposite sense. [46] Subsequently, the virus utilizes the negative-strand RNA to generate new positive RNA molecules, facilitating the subsequent phases of translation and replication to form the genomes of the latest viral particles. In SARS-CoV, topoisomerase III-beta plays a role in controlling this process. The progression of these stages can be impeded by the budding and assembly of the encapsulated virus through the use of reverse transcription inhibitors. [47] Since post-translational modification is required, the structural protein complexes M, N, E, and S, produce sub-genomic RNA before joining the endoplasmic reticulum. [48] N- structural protein produces a nucleoprotein complex and positive-strand RNA in the cytoplasm. Both complexes work together to replicate the virus in the endoplasmic reticulum-Golgi apparatus compartment (ERGIC). [49] They are released from cells and discharged into the extracellular zone via the vesicles and Golgi apparatus as mature viruses further infecting other cells. [50]

### 3. Vaccines Targets for SARS-CoV2

Like other viral diseases, vaccination is the leading way to avoid COVID-19. Several vaccine platforms have been created since the SARS-CoV-2 emergency, and as on July, 2022, about 40 vaccines received global approval. Mainly, 196 vaccines are in preclinical trials, while 153 vaccines reached the clinical trials. The currently licenced vaccines are based on protein subunits ( $n = 16$ ), inactivated virus ( $n = 11$ ), nonreplicating viral vectors ( $n = 7$ ), RNA ( $n = 4$ ), DNA ( $n = 1$ ), or viruslike particles (VLPs) ( $n = 1$ ), Figure 2. The WHO issued Emergency Use Listing (EUL) for ten of these vaccinations, which are mentioned. [51,52] Vaccines utilizing protein subunits consist of antigenic fragments from pathogens, effectively preventing human viral infection. [53] However, they lack the full antigenic complexity of the virus, limiting their efficacy as protection may be reduced due to a limited number of viral fragments. [54] Examples of protein subunit vaccines, such as COV0VAX (produced by Serum Institute of India), Novavax formulation, and Nuvaxovid (Novavax), involve the recombinant nanoparticle S protein linked to the Matrix-M adjuvant. The S protein has undergone stabilising modifications designed to address the underlying issue of its conformational instability. [55] The inactivated vaccines such as Covilo (Sinopharm), CoronaVac (Sinovac) and Covaxin (Bharat Biotech), based on the whole virus in cells, followed by chemical inactivation, purification, and then mixing with particular substances that act as immune cell stimulants and immune response amplifiers, like aluminium hydroxide adjuvant. [56] It is known that pathogens which have been radioactively, chemically, or thermally inactivated occasionally lose their immunogenicity, making the platform less effective than those that use live attenuated pathogens. [57] Nonreplicated viral vector vaccines approved for human use rely on animal or human replication-defective adenovirus vectors. Notably, Vaxzevria (Oxford/AstraZeneca) and Covishield, produced through the Oxford and AstraZeneca formulation by Serum Institute of India and Fiocruz-Brazil, are licensed vaccines based on the chimpanzee adenovirus expressing the SARS-CoV-2 S glycoprotein. Additionally, Ad26.COV2.S, licensed by Janssen/Johnson & Johnson, utilizes a recombinant human adenovirus type 26 vector to express the S protein in a stable form. [58] Since RNA-based vaccines have been licenced for use in humans for the first time and have shown excellent safety and effectiveness profiles, this platform is leading the way in the rapid development of vaccinations against emerging cases. [59–61] Spikevax

(Moderna) and Comirnaty (Pfizer/BioNTech) are nucleoside-modified RNA vaccines formulated with lipid nanoparticles. They encode the full-length SARS-CoV-2 S protein, modified by two proline mutations to maintain the pre-fusion conformation. Despite variances in their engineering processes, both vaccines share this key feature. As per a recent meta-analysis report, out of the majority of vaccines, 81% had an effect against severe disease, still higher than 70% after getting complete vaccination associated with a 10% minimal reduction six months after immunisation. [62] As most of these vaccines were developed using the prototype Wuhan-Hu-1 strain, they are less effective against the variant of concerns (VOCs) that have surfaced since the pandemic's inception. Therefore, to offer the best defence against these SARS-CoV-2 variations, modifications to vaccine composition to reflect the most common variant(s) of SARS-CoV-2 must be considered. Because COVID-19 vaccine-induced immunity is transient, new preventive measures that result in long-term protection are necessary.

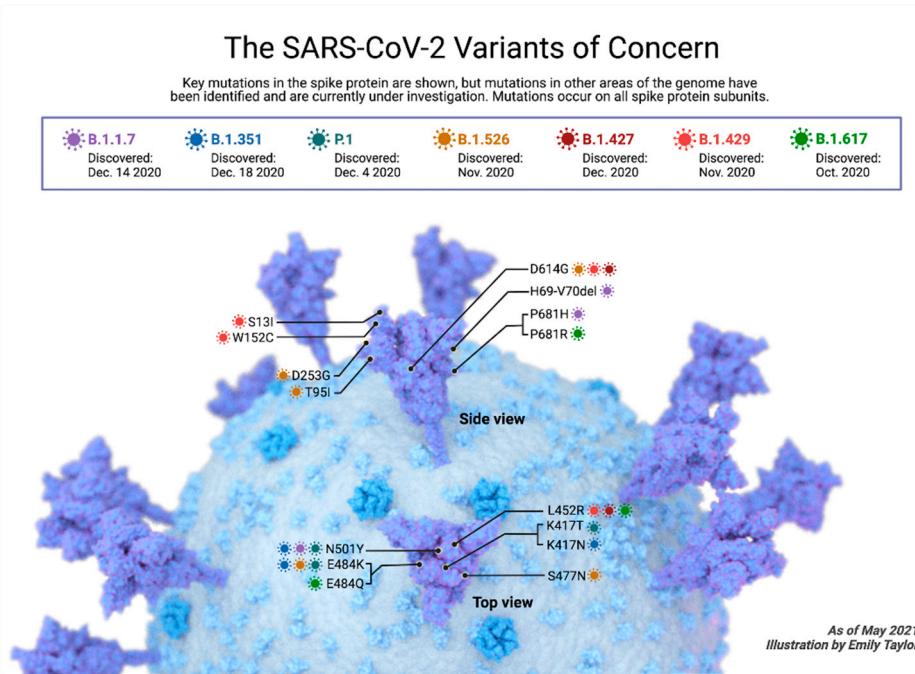


**Figure 2.** Schematic Diagram for Vaccines Candidates in human trial. Created with Biorender.

#### 4. SARS-CoV2 Variants

Once the SARS-CoV-2 virus was identified in December 2019, clinical samples from around the world have had their viral genomes sequenced daily. As a result, thousands of whole genomes have been uploaded to databanks. Due to the RdRp's limited ability to rectify errors made during genome replication, RNA viruses, including SARS-CoV-2, are known to exhibit significant mutation rates. [63] The *Coronaviridae* family is an outlier, though, as these viruses have exoribonuclease moiety that may perform proofreading as part of their machinery replication. [64] Additionally, SARS-CoV-2 was shown to have this moiety as part of its nsp14 nonstructural protein. [65] Published studies of several genomes revealed that SARS-CoV-2 had a low nucleotide diversity throughout the world. As long as the viral incidence rises, the nucleotide diversity also tends to rise. [66] The variants of SARS-CoV-2, which are genetically distinct from the initial SARS-CoV-2 lineage, have emerged as a result of virus mutation over time. These mutations may benefit the variations carrying them, boosting viral

adaptation, or they may be phenotypically neutral, having little to no significant effects on viral biology. [67] The D614G mutation on the S protein was present in the first significant variation of the identified Wuhan reference strain. After being discovered in March 2020, this mutation quickly spread throughout the world and was found in most of the current viral lineages in circulation. D614G mutation benefits the virus during replication, which could account for its quick global spread. [68,69] SARS-CoV-2 variants have been divided into three categories by the CDC: variants of interest (VOIs), variants of concern (VOCs), and variants of high consequence (VOHCs). Variants of interest (VOIs), are mutations that are believed to alter the diagnostics, treatments, transmission, or sensitivity to antibodies created after prior exposure or immunisation. They are variants with low prevalence or dispersal. In order to qualify as variants of concern (VOCs), a substance must show increased incidence or transmission, diagnostic or therapeutic failure, or diminished neutralisation by antibodies developed following prior exposure or immunisation. Variants of high consequence (VOHCs) are those for which medical treatments or preventative measures are proved less effective. Since the pandemic began, SARS-CoV-2 mutation has been shown by the recurrent discovery of several variations. [70] There are five SARS-CoV-2 variants, alpha, beta, gamma, delta, and omicron, categorised as VOCs. [70–72] CDC has not yet designated any variant as a VOHC. The D614G mutation is present in these variations, contributing to increased virus replication in the upper respiratory tract and higher transmissibility. [69,72] The World Health Organization (WHO) established these variants. [73] The variants of concern (VOCs) are outlined as follows (Figure 3):



**Figure 3.** The SARS-CoV-2 Variants of Concern. Created with Biorender.

The emergence and evolution of SARS-CoV-2 variants have significantly impacted the trajectory of the COVID-19 pandemic. The alpha variant, initially identified in the UK as VUI-202012/01, designated B.1.1.7, and subsequently referred to as alpha by the WHO, demonstrated increased transmissibility, higher viral loads, and a longer infectious period. Associated with elevated mortality, the alpha variant posed challenges for detection due to S gene target failure (SGTF). Notably, it exhibited resistance to certain vaccines and therapeutic monoclonal antibodies. The beta variant, B.1.351, originating in South Africa, showcased enhanced transmissibility and decreased neutralization by both convalescent sera and vaccines. The gamma variant, P.1, identified in Brazil, presented heightened transmissibility, increased viral loads, and potential impacts on herd immunity. The delta variant, B.1.617.2, contributed significantly to global transmission, displaying higher transmissibility and resistance to neutralization by certain antibodies and sera. Lastly, the omicron variant, B.1.1., emerged in Botswana and South Africa, marking the fourth wave of the

pandemic. Characterized by distinct biological traits, including strong ACE2 receptor binding, exceptional transmissibility, environmental stability, and resistance to authorized monoclonal antibodies, the omicron variant poses new challenges to global efforts in combating COVID-19. The continuous monitoring of these variants, their interactions with existing treatments and vaccines, and the development of targeted interventions remain imperative for effective pandemic management.

JN.1, which first appeared in Denmark at the end of July, has quickly crossed international borders and been detected in a number of nations, including the United Kingdom, Canada, the United States, South Africa, Portugal and Sweden. Numerous mutations inside the spike gene set this version apart and further complicate our knowledge of the virus's activity. The WHO has made a noteworthy advancement in the fight against the virus by classifying the unique strain JN.1 as a "variant of interest." This designation highlights the strain's potential importance. [74]

#### 4.1. Alpha SARS-CoV-2 Variant

After epidemiological and genomic surveillance, the UK revealed a SARS-CoV-2 variant in December 2020. It was initially identified as VUI-202012/01 as the first variant under investigation. [75] This variant was dubbed as B.1.1.7 according to Pango lineages; however, the WHO refers to this as alpha. It genetically differs from other variants by 23 nucleotide modifications, including 14 nonsynonymous substitutions, 6 synonymous substitutions, and 3 deletions. [76] The alpha variant, which over time became the most common in the UK and was linked to higher mortality, was believed to be more transmissible than earlier variants. [77,78] Depending on the model used to calculate the statistics, the alpha variation replication has moved from 43% to 90% more than prior variants in the United Kingdom and others. Recently, research has suggested that either a longer infectious period or more viral loads may be responsible for increased transmissibility. [77] Patients who have the alpha variant infection have shown high viral RNA levels and longer-lasting virus positive. [79,80] Due to nucleotide deletion inside the S gene of the viral genome, several commercial RT-qPCR kits targeting the S gene were unable to detect infection with the alpha version, known as S gene target failure (S) SGTF. [81] Funk et al. had observed an increased risk of hospitalisation for European patients, classified age groups as 20–39 and 40–59 years, as well as a higher risk of ICU in the age group of 40–59 years, using the SGTF, which is a method to distinguish the alpha variant from others. [82] Recent research has revealed that SARS-CoV-2, the alpha variant to a significant probability of death of about 60% in the infected patients. [78,83] The alpha variant's S protein mutation has also been associated with decreased neutralisation through the monoclonal antibodies. [84,85] They appear to have mild to no effect on the viral neutralisation from vaccine recipients. [84–87] It was demonstrated that the efficiency of the mRNA-based vaccines mRNA-1273 (Moderna) and BNT162b2 (BioNTech, Pfizer) against the alpha VOC were comparable to that of the prior variety. [88,89] Alpha variant was shown to be resistant to the inactivated-virus-based vaccines BBV152/COVAXIN (Bharat Biotech), and BBIBP-CorV (Sinopharm) [90,91] whereas CoronaVac (Sinovac) significantly decreased the neutralisation capability against this variation by a 0.5 factor. [91] While the general effectiveness of AZD1222 in both symptomatic and asymptomatic cases remained at 61.7% against the alpha variant and 77.3% against other variants, the nonreplicative-viral-vector-based vaccines, ChAdOx1 nCoV-19/AZD1222 (Oxford, AstraZeneca) and Ad26-COV2.S (Janssen), exhibited diminished neutralization capability against the alpha variant. [92] Ad26-COV2.S has not yet been tested for its effectiveness in avoiding COVID-19 brought on by the alpha version. The Gamaleya Institute's Sputnik V Ad26/Ad5 can still neutralise the alpha form. [93]

#### 4.2. Beta SARS-CoV-2 Variant

Researchers from South Africa described another variation of SARS-CoV-2 that appeared following the initial epidemic wave in the same month of the initially detected alpha variant in the UK, [94] initially known as S501.V2, was referred as B.1.351 by Pango lineages and beta by the WHO. When the beta VOCs was initially identified, it had 31 mutations, four of which were also present in the B.1 variant. There are 21 nonsynonymous mutations among the 27 unique variations reported in this lineage, while 12 have been fixed in the variant population over time. [94] The N501Y alteration

on the S protein, critical for viral phenotype, is shared by this developing variation and the alpha VOC. Beta VOC was exhibited to be 50% more transmissible than previously circulating versions. [95] When compared to non-VOCs, beta VOCs were associated with increased risk of hospitalisation in European patients in the categorized aged 40-59 and 60-79 years, as well as ICU with 40-59 year age group, although this did not increase deaths. [82] Beta VOC's decreased sensitivity to neutralisation by recuperating and vaccine-elicited sera appears to be its most significant trait to date. The ability of the mRNA-1273, BNT162b2, BBIBP-CorV, CoronaVac, ChAdOx1, Sputnik V Ad26/Ad5 and nCoV-19/AZD1222 vaccines to neutralise this variation was less effective. [85,86,91,93,96-100] For example, ChAdOx1 nCoV-19/AZD1222, [100] BNT162b2 appears to preserve its efficiency to prevent severe forms of the disease, despite a considerable decline in vaccination efficacy being seen in a population-based investigation. [88] According to assessment report EMA/158424/2021, the vaccine BBV152/COVAXIN and Ad26.COV2.S were evaluated to be effective against beta VOC. [101] This variant decreased neutralising by therapeutic monoclonal antibodies. [86,99] Therefore, the beta VOC needs to be continuously monitored by genetic monitoring as it may be linked to an increase in the frequency of reinfections and the failure of vaccines or treatments.

#### 4.3. *Gamma SARS-CoV-2 Variants*

Another SARS-CoV-2 variation, known as P.1 (gamma) was discovered in Manaus, Brazil, in December 2020, which may have contributed to a significant rise in COVID-19 prevalence. Initially, this gamma variant was identified by 35 mutations dispersed throughout the entire genome. The S gene contains 10 nonsynonymous mutations, of which 3; K417T, E484 K, and N501Y, are shared with the variant B.1.351 and one, N501Y is shared with both B.1.1.7 and B.1.351 variants. [102] The gamma VOCs were the predominant variety in the city in January 2021 due to their estimated transmissibility, which was 1.7 to 2.5 times more than those of non-gamma variants circulating in Manaus. [102,103] The increased in viral loads was also observed in gamma variant-infected individuals, which may play a role in the more infectious behaviour of this variant. [103] Gamma variant infection was linked to a significant probability of hospitalisation and ICU admission. [82] The emergence of this variant may also be a factor in the reinfection patients [104,105] and the recurrence of disease in regions where previous variants likely contributed to herd immunity. [106] When neutralised by convalescent plasma and therapeutic monoclonal antibodies, the gamma variant is only partially to entirely susceptible. The vaccines mRNA-1273 and BNT162b2 fared the best, with slight to moderate declines in their ability to neutralise this variation. [104,107-109] A patient case who had the entire BNT162b2 vaccination and experienced modest symptoms following gamma infection was documented. [110] CoronaVac's effectiveness against gamma was estimated, and AZD1222's ability to destroy this virus was diminished. [109]

#### 4.4. *Delta SARS-CoV-2 Variant*

It is reported in India an upsurge in COVID-19 cases in December 2020 and the first few months of 2021, attributed to the appearance of the SARS-CoV-2 variants B.1.617.1, B.1.617.2, and B.1.617.3 which were transferred to other countries. [111] Delta variant B.1.617.2 created a community transmission chain in many countries around the world and quickly increased its share, becoming the dominant lineage there. [111,112] The delta VOC was predicted to become the main circulating lineage until the development of the omicron variation, with a reproduction number 97% higher than the observed number for non-VOCs and at least 30% more than those for other VOCs. [112] This variant has 12 nonsynonymous mutations, 5 of which are in the S gene. The enhanced transmissibility of the delta variant may be attributed to increased viral loads, presumably due to a faster replication rate than other variants. [113-115] The two spike mutations T478K and L452R, present in this variation, are projected to enhance its interaction with ACE2 and may increase the virus's capacity to penetrate human cells, although this prediction has to be verified. A higher likelihood of hospitalisation and disease severity were connected to the delta VOC. [113,116] The delta VOC is resistant to neutralisation by several therapeutic monoclonal antibodies and convalescent sera, as reported for other VOCs. Additionally, The BNT162b2-vaccinated sera showed a diminished ability

to neutralise the delta variant, particularly after partial immunisation. Complete BNT162b2 vaccination appears to produce immunity against delta vs. other SARS-CoV-2 variants. [117–120] In reality, based on studies, [120,121] complete immunisation was equally effective against the delta VOC and the variant B.1.1.7. The protection provided by the mRNA-1273 immunisation against the emergence of symptomatic cases resulting from delta infection was inferior to that provided by B.1.1.7 infection. However, mRNA-based vaccines, BNT162b2 and mRNA-1273 examined collectively effectively prevented the onset of mild to severe disease in vaccinated subjects. [122] In a Chinese population, The effectiveness of several inactivated-virus-based vaccinations, such as CoronaVac's inactivated COVID-19 vaccine, Sinopharm's HB02 and WIV04, and Biokangtai's inactivated COVID-19 vaccine, were assessed collectively. They achieved 100% efficacy against severe diseases and 69.5% efficacy against pneumonia associated with COVID-19. [123] The amount of the delta variation that BBV152/COVAXIN-elicited sera were able to neutralise shows that these sera's potency against this strain was only slightly diminished. [124] Nonreplicative-viral-vector-based vaccinations impaired the ability of sera to neutralise the delta VOC. [86,117,125,126] There is need for more research because the effectiveness of AZD122 as determined by population-based studies varies. [120,121]

#### 4.5. Omicron SARS-CoV-2 Variant

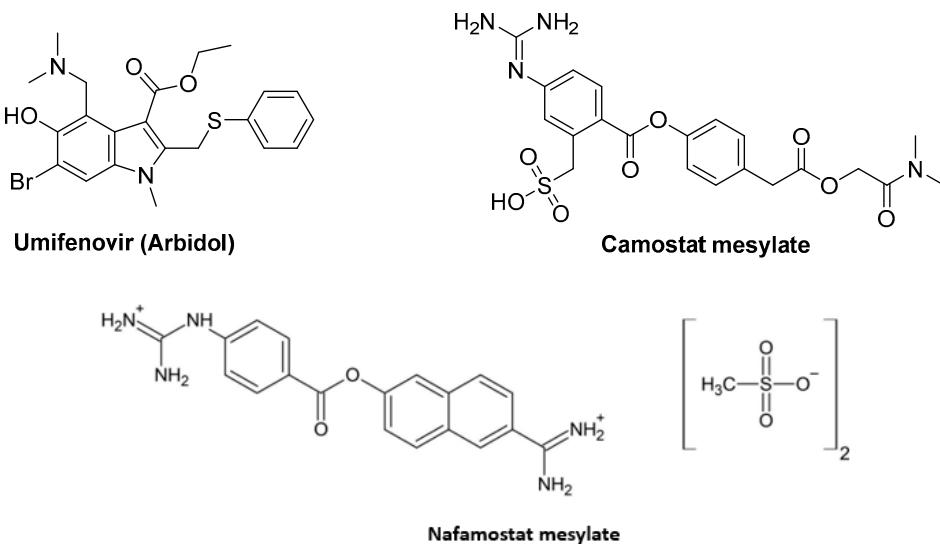
The SARS-CoV-2 omicron variant B.1.1., originally appeared in Botswana and South Africa and has been linked to a significant increase in the COVID-19 pandemic; on November 26, 2021, the WHO categorised it as a VOC. Its appearance has caused the COVID-19 pandemic's 4th wave to spread globally. [127,128] The omicron VOC exhibits distinctive biological traits, such as strong binding to the human ACE2 receptor and great transmissibility. The omicron VOC also exhibits excellent environmental stability, high resistance to monoclonal antibodies that clinical trials have authorised, and immunity produced by natural infection or vaccination. The SARS-CoV-2 omicron variant and a number of its traits have been updated. [127,128]

### 5. Antiviral Drugs against COVID-19

#### 5.1. Fusion Inhibitors Targeting Spike Protein

##### 5.1.1. Umifenovir (Arbidol)

A short indole derivative called umifenovir, Figure 4, has a variety of anti-RNA and anti-DNA viral effects. They inhibits viral internalisation or attachment and blocks viral penetration into the host cell. [129] It is authorised to prevent and cure influenza A and B infections, in China and Russia. [130,131] However, *in vitro* studies have shown activity against viral illnesses, including Hepatitis B and C viruses (HBV and HCV) and Ebola. Umifenovir was first authorised for influenza treatment in Russia in 1993. The drug is available in China and Russia for the treatment of upper respiratory influenza A and B infections. [132] Umifenovir is advised for COVID-19 patients in the "Treatment Scheme and New Coronavirus Pneumonia Diagnosis." Adults receive 0.2 g of drug three times per day for ten days. [129] In clinical trials, umifenovir, orally administrated, was found to reduce mortality and viral load in contrast to other unnamed antiviral medications or the interferon-only control group. [133] It includes mild general adverse effects such as, nausea, headaches, raised bilirubin, leukopenia, and high alkaline phosphatase (AKP) and other symptoms like abdominal pain. No notable side effects were observed during treatment, according to retrospective studies to assess the safety and effectiveness of umifenovir therapy in COVID-19 patients. [129]



**Figure 4.** Chemical structures of Fusion inhibitors that target S spike protein; Umifenovir, Camostat mesylate, and Nafamostat mesylate.

### 5.1.2. Camostat Mesylate

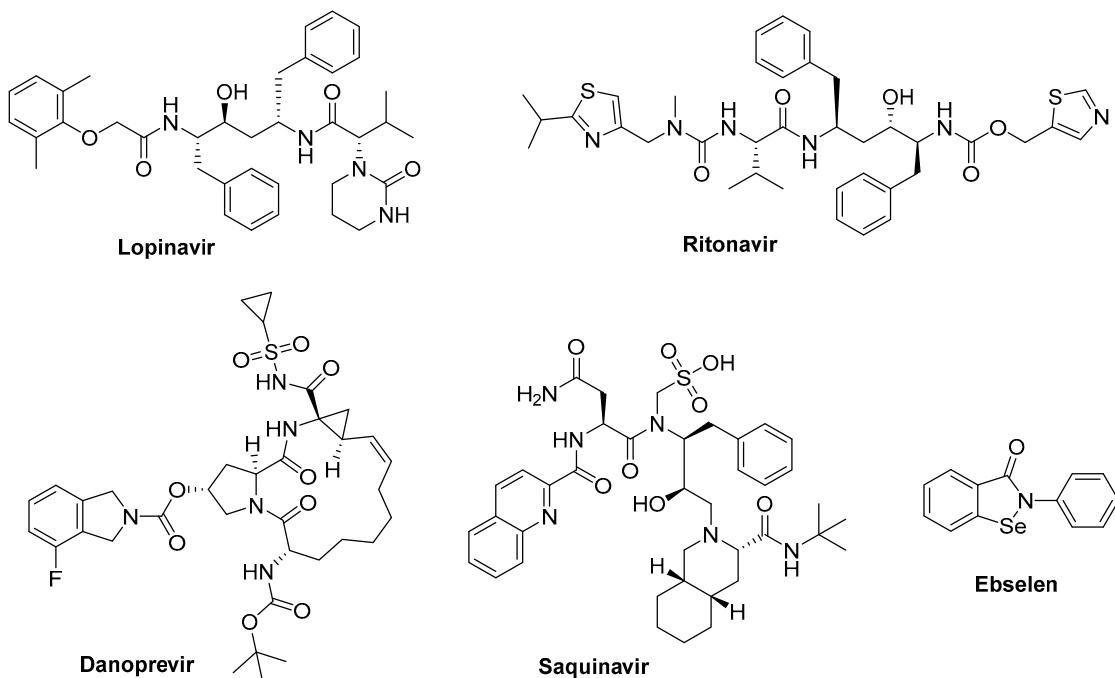
Camostat mesylate, figure 4, another drug that targets virus fusion, is a serine protease inhibitor. [134] For target cells entry; SARS-CoV-2 binds to TMPRSS2 and/or ACE-2 receptors within the targeted host cells. [135,136] Camostat mesylate works by inhibiting TMPRSS2. [137] The SARS-CoV-2 spike (S) protein is downregulated to prevent the virus from entering the cell and thereby preventing surface fusion. [138] An earlier study found that camostat mesylate prevented SARS-CoV from entering human epithelial bronchial cells. [139] *In vitro* studies revealed that camostat mesylate and E-64d, a cysteine protease inhibitor, effectively inhibit SARS-CoV-2 TMPRSS2. [35] In Denmark and Germany, the effectiveness of hydroxychloroquine and camostat mesylate combination therapy has been evaluated. [50] Serine protease inhibitor, nafamostat mesylate, was found to have a 15-fold higher effectiveness for SARS-CoV-2 viral entrance into the host cells. Because nafamostat has more effective antiviral action and a good safety profile, it may be considered a safer alternative to camostat mesylate. Additionally, nafamostat mesylate is used to treat disseminated intravascular coagulation (DIC) with enhanced fibrinolysis seen in COVID-19 patients. [50]

## 5.2. Protease Inhibitors

### 5.2.1. Lopinavir

In combination with lopinavir (Figure 5), Ritonavir is used for HIV infection treatment. Additionally, it has been shown that lopinavir inhibits SARS-CoV-2 replication with an EC50 of 2.660/1.671  $\mu\text{M}$  ratio. [140] Half-maximal effective concentration (EC50). The number of eosinophils increased among COVID-19 cases after it was administered in China as an emergency medication. [141] Ritonavir and lopinavir, as HIV protease inhibitors, have shown encouraging results as SARS-CoV-2 major protease (Mpro) inhibitors in an *in vitro* investigation. [11] An earlier investigation revealed that the drug kaletra®, a specific lopinavir/ritonavir combination, has antiviral activity against the SARS-CoV *in vitro* and clinical studies. [142] As a result, this combination is also employed as a backup plan for COVID-19 patients. An earlier investigation showed that while lopinavir/ritonavir therapy was associated with better outcomes, it did not improve the patient's clinical recovery from COVID-19 infection. [143] Although lopinavir's efficacy for treating COVID-19 has not yet evaluated, but USA, Japan, and Singapore treat COVID-19 patients with such ritonavir/lopinavir combination. The lopinavir/ritonavir efficacy for COVID-19 is now being studied in clinical trials in many countries such as France, Spain, Thailand, China, Hong Kong, Canada, and the United States. [50] Furthermore, according to the WHO, a "solidarity" clinical trial for coronavirus

was conducted using an inflammation-regulating molecule, interferon (INF)- $\beta$  alone or with lopinavir/ritonavir. [140] Additionally, patients with COVID-19 can experience improved clinical symptoms and a lower viral loads when using the lopinavir/ritonavir combination. [133]



**Figure 5.** Chemical structures of Protease inhibitors Lopinavir, Ritonavir, Danoprevir, Saquinavir, Ebselen.

### 5.2.2. Lopinavir/Ritonavir + Ribavirin

Ritonavir (RTV) and lopinavir (LPV), (figure 5) are the protease inhibitors suggested in a combined form (Kaletra®) which is a HIV medication. [20,129] Because lopinavir inhibits the HIV protease, [144] may reduce the virus infection rate and interfere with the development of mature virus particles. Lopinavir has a short half-life and a limited bioavailability. [129] Lopinavir, an HIV protease inhibitor, can affect the maturation of viral particles and reduce the virus's ability to spread. Conversely, Ritonavir blocks the cytochrome CYP3A4 enzyme, slows down the cytochrome P450 and reduces the lopinavir metabolism. The bioavailability of lopinavir *in vivo* can be increased by administering ritonavir and lopinavir together. [16,129,145] Ribavirin is a guanosine analogue that inhibits the RdRp-mediated elongation of viral RNA chains. [20] The bioavailability and *in vivo* antiviral activity of lopinavir are markedly increased by the combination of lopinavir and ritonavir. Compared to Remdesivir, prophylactic ritonavir/lopinavir-interferon was somewhat effective at reducing the viral load for MERS-CoV infection in mice. However, there were no significant post-infection effects on acute lung injury, viral load, or lung haemorrhage. [146] 400 mg/100 mg of lopinavir/ritonavir each can be taken every 12 hours for a minimum of 10 days and a maximum of 14 days. The entire dose of 400/100 mg is prescribed for children at a rate of 10 mg/kg for children weighing 15–40 kg and 12 mg/kg for children weighing 7–15 kg. Interferon- $\beta$  is administered in conjunction with ritonavir/lopinavir on a 44 g for three doses every six days if the history of symptoms is less than seven days. [147]

### 5.2.3. Lopinavir/Ritonavir + Umifenovir

Compared to lopinavir/ritonavir alone, patients who got the triple combination therapy of lopinavir/ritonavir along with umifenovir demonstrated an advantage in preventing the onset of illness. In addition, the progression of lung injury was dramatically halted by the ritonavir/lopinavir and umifenovir combination. [50]

#### 5.2.4. Danoprevir

Hepatitis C protease activity is effectively inhibited by danoprevir (figure 5). [148,149] By 2018, it had been authorized in China as an oral antiviral drug to treat hepatitis C. As a result, it was called a repurposed drug COVID-19 treatment. A triple combination of pegylated-interferon- $\alpha$ , ritonavir-boosted danoprevir, and ribavirin demonstrated a sustained virologic response within 12 weeks (SVR12) in Chinese patients infected with non-cirrhotic hepatitis C virus. [150] In both phase II and III clinical trials, the SVR12 rate for infected cases approached 99% when utilizing this triple combination of ribavirin, ritonavir-boosted danoprevir, and ravidasvir, an HCV NS5A inhibitor, as part of the entire oral administered therapy for non-cirrhotic HCV. [151]

#### 5.2.5. Darunavir

The treatment of COVID-19 in Italy has been suggested using the anti-HIV medication darunavir. In a regimen, it may be used with cytochrome P-450 inhibitors like cobicistat or ritonavir. Additionally, good anti-proliferative results against SARS-CoVs have been observed in *in vitro* studies. [152] In Thailand, a clinical investigation is underway to evaluate the effectiveness of darunavir in combination with other agents like hydroxychloroquine and antivirals for coronavirus patients. Additionally, a clinical trial in China explored the combination of cobicistat and darunavir. Consequently, prezobix®, a fixed-dose combination of cobicistat and darunavir, could potentially be utilized in the treatment of COVID-19 patients. [50] Recently, HIV-positive individuals already on darunavir medication were exposed to COVID-19, prompting interest in the efficacy of this HIV protease inhibitor (146). However, darunavir may not be effective in preventing SARS-CoV-2 infection at the currently recommended dose of 800 mg. [50]

#### 5.2.6. Atazanavir

According to an *in-silico* investigation, atazanavir is more potent than lopinavir at the binding site in SARS-CoV-2 Mpro. Furthermore, an *in vitro* investigation demonstrated that atazanavir suppressed SARS-CoV-2 replication. [153] Ritonavir/atazanavir use is linked to higher lipid parameters and glucose absorption when compared to lopinavir/ritonavir use, according to research on HIV-infected individuals. [154] Studies show that Atazanavir could substitute for lopinavir, as Atazanavir when combined with ritonavir, will have the same effect as lopinavir alone. [155]

#### 5.2.7. Saquinavir and Other Protease Inhibitors

Saquinavir (figure 5) and other protease inhibitors, including nelfinavir, amprenavir, indinavir, and nelfinavir, serve similarly against COVID-19 as protease inhibitors due to the similarity between their chemical structures. [156] Saquinavir and indinavir were found to inhibit 3CLpro activity in SARS-CoV-2 in *silico* investigation. Another study discovered that indinavir, saquinavir, nelfinavir, and amprenavir suppressed SARS-CoV-2 *in vitro*. [157] Saquinavir, however, provides the most potent inhibition when compared to the other drugs. The drug saquinavir has been used to treat COVID-19 patients in Singapore. In a separate *in silico* investigation, two more possibilities, raltegravir, and paritaprevir, were investigated and showed inhibitory effects on the SARS-CoV-2 3CLpro. [158] Through current screening of medicinal plant libraries, potent anti-viral phytochemicals that may function as inhibitors against SARS-CoV-2 3CLpro have been discovered. [159,160] As a result, further *in-vitro* investigations could be used to examine the reported antiviral agents. [50,158]

#### 5.2.8. Niclosamide

Niclosamide, an FDA-approved anthelmintic drug, is employed for the treatment of various viral infections spanning from nanomolar to micromolar concentrations. These infections include Zika virus (ZIKV), hepatitis C virus (HCV), Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV), Ebola virus (EBOV), Chikungunya virus (CHIKV), Japanese encephalitis virus (JEV), and human adenovirus (HAdV).

Due to its cost-effectiveness and minimal *in vivo* toxicity profiles as an FDA-approved drug, niclosamide holds the potential to be a valuable therapeutic agent in combating the escalating COVID-19 pandemic. [161] Screening studies of a small commercialised pharmacological library show that niclosamide might stop the replication of SARS-CoV and viral antigen. [162] Niclosamide prevented the SARS-cytopathic CoV's effect (CPE), which in turn prevented the virus from replicating in Vero E6 cells. The SARS-CoV 3CLpro is a key tool for identifying anti-SARS drugs and plays a significant role in synthesizing polyproteins. [163–165] 2-chloro-4-nitroaniline compounds were discovered to be effective SARS-CoV 3CLpro inhibitors. Up to 50 M, niclosamide had no overt inhibitory activity against SARS-CoV 3CLpro. Additionally, after 48 hours post-infection, studies have shown that niclosamide reduces MERS-CoV replication.

#### 5.2.9. Nelfinavir

Nelfinavir is an antiviral drug that uses different mechanisms to target HIV. It is an inhibitor of HIV-1 protease. The mechanism of action of nelfinavir involves binding to the HIV-1 protease active site and inhibiting the processing of functioning proteins required for HIV. According to the *in vitro* studies conducted during the SARS pandemic, Nelfinavir was identified as a potential agent with SARS-CoV inhibitory effects. [166] Out of the 30 examined drugs, nelfinavir provides the most potent protective effect against SARS-CoV-2. Its efficacy against SARS-CoV or SARS-CoV-2 in humans has not yet been investigated. The recommended dose for HIV is 1250 mg or 750 mg orally twice a day. However, the required dose for COVID-19 therapy is uncertain. [167] Pharmacokinetics of nelfinavir in chronic hepatic disease patients can be varied. [168,169] It causes gastrointestinal intolerance, including nausea, and diarrhoea. [167]

#### 5.2.10. Ebselen

Serving as peroxiredoxin mimic enzyme and glutathione peroxidase, ebselen, (figure 5) is an organoselenium substance that reduces peroxynitrite and hydroperoxides. [170] Ebselen interacts with certain thiols protein via a selenosulfide link, leading to anti-inflammatory, pleiotropic, and antibacterial effects in addition to its antiviral activity. Regarding the SARS-CoV-2 Mpro is a potential therapeutic target, ebselen had been identified as over 10,000 chemicals panel as a prospective inhibitor of Mpro. The role of Ebselen is to identify cysteine proteases in viral and other microbial infections and influences lung inflammation. Ebselen can also be used as a lead target to suppress SARS-CoV-2 Mpro effectively, and *in vivo* adherent cell studies have shown that it has inhibitory effects. Therefore, COVID-19 attributes possible benefits to the critical pathogenetic goals of modulating cytokines and inflammatory oxidants. [140] Diverse biological pathway targets, such as enzymes linked with inflammatory reactions, were found in early studies of ebselen for clinical diseases. [171–173] No adverse effects have been observed in scientific investigations. [174] Eliminating selenium is then excreted and degraded as methylated conjugates and glucuronidated. [140,175] Ebselen also possesses anti-inflammatory activity *in vivo*, suggesting that it may have a vital role in host responses to viral infections. [129] Furthermore, it prevents the formation of oxidised substances in brain tissue caused by encephalitis HIV and Simian immune deficiency virus encephalitis in macaques. [135] The idea is to use ebselen's therapeutic properties to stop the signs of a neurological HIV-1 infection in the brain.

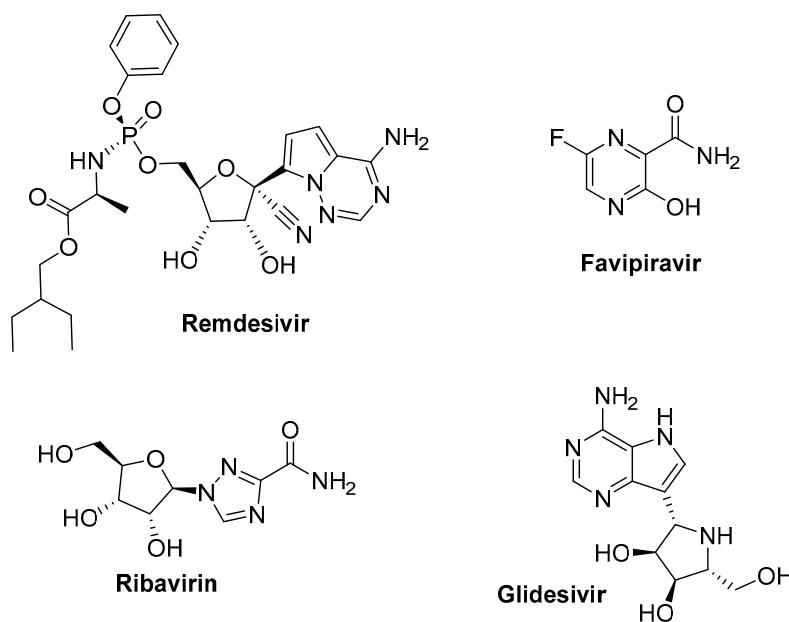
### 5.3. RNA-Dependent RNA Polymerase Target, Reverse Transcriptase Inhibitors

#### 5.3.1. Remdesivir (GS-5734, Veklury) (Gilead Sciences)

Remdesivir, depicted in Figure 6, stands as the first authorized drug specifically developed for the treatment of Ebola. [176,197] Ebola, being a single-strand RNA virus, faces inhibition from Remdesivir, which acts as an adenosine analogue. This inhibition targets the viral RNA-dependent RNA polymerase (RdRp), leading to either premature or delayed RNA chain termination. [20,177–179] Notably, Remdesivir has demonstrated antiviral activity against respiratory viral infections, including SARS-CoV-2, in *in vitro* settings. [180] *In vivo* experiments involving SARS-CoV and

MERS-CoV-infected animals revealed reduced airway inflammation and improved lung function, showcasing similar protective effects. The efficacy of post-exposure therapy is contingent on the timing of Remdesivir administration. [20] Furthermore, the licensing of nucleoside analogues for treating both DNA and RNA viruses is crucial in comprehending the mechanism of action underlying Remdesivir. However, several nucleoside analogue inhibitors have been observed to be ineffective against CoVs. [181,182] Remdesivir, a nucleoside analogue, works as an RdRp inhibitor by concentrating on the viral genome involved in viral replication. In the RdRp process, it thereby inhibits the protein complex of CoVs. The host breaks down Remdesivir to its active metabolite nortriptyline (NTP), which is then conjugated to ATP and incorporated into the developing RNA strand. Inclusion of a new strand stops the RNA synthesis and the expansion of the RNA strand once nucleotides are added. All CoVs include a proofreading process that detects and removes other nucleoside analoge activity, keeping antiviral activity. Surprisingly, it has been discovered that the mutant Murine hepatitis virus (MHV) lacked proofreading capabilities and was hence highly vulnerable to Remdesivir. It is also likely that mutations that enhance proofreading or base-pairing precision will result in Remdesivir resistance. Some data suggested that Remdesivir might work via a different mechanism, permitting partial antiviral vitality to endure despite viral changes. [182] WHO has authorized/approved the emergency use of Remdesivir. WHO revised its conditional advice against Remdesivir in hospitalised patients in November 2020 and is not recommended in this situation under any circumstances. [183] Phase III clinical research on Remdesivir is crucial for obtaining the more potent antiviral drug to combat this outbreak. [184] Clinical trials in 36 of 53 patients show appropriate data in 61 hospitalised patients taking Remdesivir off-label. However, without a placebo group, these findings are difficult to comprehend. An initial randomised controlled trial was flawed, favouring Remdesivir with a non-significant trend toward shorter time to clinical changes. This trial was insufficient, however it did show that patients treated with Remdesivir had better healing as an average recovery time of 11 days vs. placebo of 15 days. In addition, there were improvements for better survival on day 14. The research indicated disadvantages in individuals with high-flow oxygen, and invasive or non-invasive ventilation, indicating that antivirals like Remdesivir might have a poor impact in late diseases where the phenotype is likely to be inflammatory. The analysis was published before the full results could be obtained via follow-up research. [20] Remdesivir is now the subject of several clinical research studies regarding COVID-19 prevention. An initial dose of 200 mg of intravenous Remdesivir is given to participants in this double-blinded, placebo-controlled study on the first day, followed by a controlled dose of 100 mg per day and up to a maximum of 10 cumulative days of treatment before release. The initial trial result is expressed as the percentage of patients in each group, employing a seven-category clinical severity scale, up to the fifteenth day following the initiation of therapy, as indicated by the United States National Library of Medicine clinical trials registry. Gilead Sciences is also supporting a Remdesivir study in patients with severe COVID-19 that will combine a primary outcome test of fever with an outcome test of oxygen normalization. In Hubei Province, China, two double-blind placebo-controlled trials included patients: one for hospitalized individuals with mild-to-moderate COVID-19 and the other for severe cases. [178] In the mild-to-moderate study, key success criteria include the normalization of body temperature, oxygen consumption, breathing rate, and cough recovery for a minimum of 72 hours. Timing for health advancement is the key outcome in the extreme case study, which is presented using a six-category ratio scale from discharge to fatality. [178] It is described that Remdesivir was also found to be effective against MERS-CoV, reducing viral loads in the infected mice and restoring normal lung-based function. [185] Additionally, it is regarded as a treatment-assist agent for SARS-CoV-2. [176] The viral load in oropharyngeal and nasopharyngeal swabs could be reduced by Remdesivir treatment for about 12 days, according to preliminary studies. [87] The combination of Chloroquine, an anti-malarial drug, and Remdesivir, can successfully stop the growth of SARS-CoV-2 in Vero E6.86 cell lines in an in vitro studies. The potential effect of Remdesivir in COVID-19 is being studied in clinical trials in France, USA, and Norway. Remdesivir was used in treatment in Singapore and the USA and injected intravenously into the first patient who recovered there. [186] In a different research, 584 participants received

Remdesivir or continued receiving conventional therapy, and 533 (91%) of these patients finished the experiment. Patients in the 5-day Remdesivir group received an average of 5 days of treatment, while those in the 10-day Remdesivir group received an average of 6 days. Compared to patients getting standard therapy, patients in the 5-day Remdesivir group showed statistically noticeably higher probabilities of a better clinical status distribution on day 11. [187] However, trial outcomes regarding safety, secondary outcomes, and viral load showed 22 of 158 Remdesivir patients died (14%), compared to ten of 78 placebo patients (13%), and there was no evidence that viral load declined differently over time in the placebo groups and Remdesivir. [188] Remdesivir's limited oral bioavailability often limits its preventive use. Additional pharmacological measures are required to make the drug available to the outpatient population. Remdesivir inhalation Phase 1 trial and FDA approval were recently reported by the manufacturer. [189] During clinical trials, Remdesivir was administered as a freeze-dried powder injection. The dosage technique employed is as follow; on the first day, an initial dose of 200 mg of Remdesivir is supplied via intravenous dripping. Then, for the next 9 days, 100 mg is supplied intravenously as a maintenance dose. [129]



**Figure 6.** Chemical structures of RNA-dependent RNA polymerase; Remedsivir, Favipiravir, Ribavirin, Glidesivir.

### 5.3.2. Favipiravir

Favipiravir is classified as a purine analogue (Figure 6) and was licensed for influenza treatment in Japan. [190] In vitro, it also exhibits selectivity against several RNA viruses, including SARS-CoV-2. Favipiravir improved the survival of the influenza A virus in mice. [20] It has been shown, *in vitro*, to be effective against oseltamivir-resistant A, B, and C viruses. In many RNA viruses, favipiravir is regarded as a substrate of viral RNA polymerase once it has been transformed to the active phosphoribosylated form. [184] The enzyme, in the tissue, phosphoribosylated it to its active form, favipiravir-RTP. The mechanism of action of favipiravir could be described as follows; (a) The RNA-dependent RNA-polymerase (RdRp) enzyme, which serves as a substrate molecule, misinterprets it for a purine nucleotide. As a result, its activity is inhibited, effectively ending the viral protein replication. [191] (b) By blocking further extension and integrating into the RNA viral chain, this mode of action, together with the catalytic domain's ability to keep the RdRp enzyme active, demonstrates the wide range of activities this molecule. [192] (c) Favipiravir is considered as a virucidal drug. During the influenza infection, it is determined to cause lethal *in vitro* mutagenesis. However, it is unclear whether Favipiravir has a similar action against SARS-CoV-2. Favipiravir is an orally administered drug with a mode of action similar to Remdesivir. There is less evidence to support the use of favipiravir. However, it is still emerging as a helpful drug within mild-to-moderate

circumstances. [193] The advantage of favipiravir is that it is administered orally. Therefore, it can be administered as part of hospital treatment for patients with symptoms that are not critical. This drug may be utilised in several cases because mild to moderate concomitant disorders are present in many COVID-19 cases and then care should be given at home. Favipiravir reduces viremia if given after the inception of COVID-19 symptoms. The effect of favipiravir on prophylaxis is also being studied in an ongoing study. [193] Heavy pill pressure, 18 tablets filled on the first day, and 8 tablets each day for the duration of the treatment term is its principal drawback. With the recent addition of a 400 mg dose, these concerns over the intense pill pressure are being partially allayed. A two-week prescription medication time is another drawback. Teratogenicity is the most significant side effect of favipiravir. Additionally, there were adverse outcomes such as neutropenia, elevated ALT and AST, diarrhoea, and increased uric acid throughout the phase III clinical investigation in the patients in Japan. The most frequent side effects of favipiravir with COVID-19 included hepatic enzyme abnormalities, psychiatric and gastrointestinal symptoms, and blood elevations of uric acid. Although pregnant women should not take favipiravir, the side effects are often mild. [129,193] In Japan, favipiravir is authorised to treat new or recurrent influenza. It was one of the first medications for COVID-19 management to be approved. [12,129,193] The recommended favipiravir dosage for influenza in China is 1600 mg given orally every 12 hours on the first day, followed by 600 mg given orally every 12 hours, and on the sixth day, 600 mg given orally every 24 hours. [129] Additionally, individuals with COVID-19 infections were enrolled in randomised trials with either interferon and favipiravir or baloxavir, marboxil, and favipiravir. [184] To determine whether the therapies work in concert or separately, umifenovir and other antivirals are frequently combined. [184] In an open-label, non-randomized study conducted in China, SARS-CoV-2 patients who received a double dose of interferon and favipiravir as opposed to a triple dose of interferon and ritonavir and lopinavir experienced viral clearance in 4 days vs. 11 days, and their chest X-rays significantly improved. [20]

### 5.3.3. Ribavirin

Ribavirin, is known as a guanosine analogue (Figure 6) with various RNA antiviral activities. [129,194] Many viral infections, including hepatitis C virus (HCV), respiratory syncytial virus (RSV), and other hemorrhagic viruses, are treated with Ribavirin. *In vitro* studies exhibited antiviral activity against SARS-CoV at 50 mg/mL concentrations. Reducing haemoglobin, which is a negative side effect that is hazardous to those who are experiencing respiratory failure. [194] Hemolytic anaemia and reproductive damage are the most severe side effects of ribavirin. [195] The antiviral activities of ribavirin entail non-specific or specific chain end-up, lethal mutagenesis, and suppression of nucleotide biosynthesis. [135] For COVID-19 patients, reported by the Chinese government, ribavirin is utilised. Adults get a dose of 500 mg administered intravenously 2 to 3 times each day for a maximum of 10 days. Ribavirin should be used with interferon or both ritonavir/lopinavir. [129] Another retrospective research followed the adverse effects, of 126 patients using 2000 mg of ribavirin as part of their treatment. Increased hemolytic haemorrhage, transaminase (40%), and bradyarrhythmia (14%) were present in certain patients. [196] Therefore, it is essential to monitor the ribavirin dose when treating COVID-19 individuals carefully. [178] During previous MERS-CoV and SARS-CoV outbreaks, ribavirin was also examined, although the results were conflicting. To stop virus replication at the micromolar stages for SARS-CoV-2, a randomised Phase II clinical trial involving 127 patients with mild to moderate COVID-19 was carried out. [197] It is more advised to combine ribavirin/interferon- $\beta$  with ritonavir/lopinavir than to use just those drugs. [198] Additionally, it has been demonstrated that anti-parasitic medications such as nitazoxanide and ivermectin enhance the effects of interferon- $\alpha/\beta$  and, consequently, the immunological responses. They were investigated for COVID-19 instances without comorbidities while using ribavirin. However, the clinical trials mentioned above are insufficient to explain how ribavirin has successfully slowed the progression of the disease. On the other hand, a Phase I evaluation showed inhaled ribavirin preparation as the sole drug in the hospitalisation of adult COVID-19 patients. [199] Tenofovir, a nuclear adenosine analogue, used to treat HIV or HBV infections that have persisted for a long time. Tenofovir's efficient integration can effectively stop the polymerase reaction into RNA-

dependent RNA polymerase. Tenofovir is regarded as a first-line substitute for HIV prevention both before and after exposure and is thought to be a very effective component of HIV-contaminated antiretroviral therapy when combined with emtricitabine. Two-randomised phase III clinical studies utilising emtricitabine/tenofovir were conducted for prophylaxis prior to the exposure of healthcare workers to COVID-19, which is inconsistent with the aforesaid therapeutic approach. [200]

#### 5.3.4. Galidesivir

Galidesivir, an analogue of adenosine, [129,194] swaps nitrogen for carbon at position 7 of a base and nitrogen for oxygen at position 1 of the ribose ring (Figure 6). [191] The structural modification alters the electrostatic interaction with the viral RNA polymerase and causes the expanded RNA strand to end prematurely. [201] Galidesivir is now being used as an antiviral treatment for Ebola and has demonstrated a wide range of antiviral activities against Flavivirus, Arenavirus, Togavirus, Bunyavirus, Paramyxovirus, Coronavirus, one Picornavirus Filovirus, and one Orthomyxovirus. [201–203] In primary human cell cultures, Galidesivir inhibits SARS-CoV, SARS-CoV-2, and MERS-CoV infection, enhancing respiratory function and reducing viral load. The antiviral studies demonstrated its capacity to integrate numerous deadly mutations via viral RNA, but not via host RNA, resulting in a significant barrier to drug resistance development. [202] Galidesivir was also shown in a pilot study to partially protect against Rift Valley Fever Virus (RVFV) infection in mice. [105] Recently, models for tick-borne Flavivirus and Zika infection have shown effectiveness. Galidesivir's phase I human research showed excellent tolerability and promising pharmacokinetics features when administered intramuscularly to healthy individuals compared to placebo. [201,204]

### 6. Other Nucleoside/Nucleotide Analogs (Transcription Inhibitors)

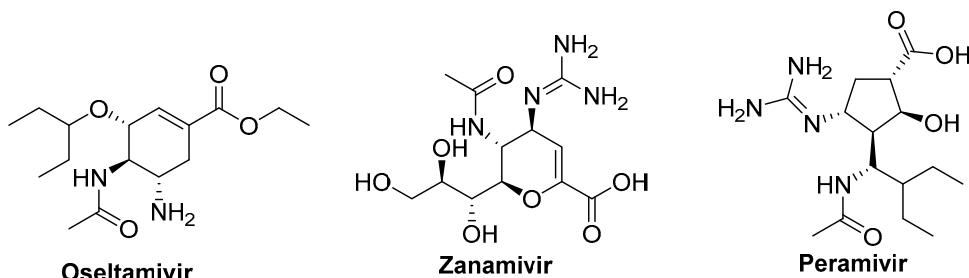
It is possible to consider other nucleoside and nucleotide analogue medications. They either focus on treating various viral infections (such as those treated with ribavirin, sofosbuvir, tenofovir, and telbivudine) or are being professionally researched (such as galidesivir, and EIDD-2801). [202] They are anticipated to have antiviral effect against SARS-CoV-2 because of their structural similarities to either ribavirin or Remdesivir. The FDA has granted authorization for certain drugs, including abacavir, alafenamide, tenofovir, didanosine, adefovir, ganciclovir, disoproxil, and tenofovir, as Nucleoside Analog Reverse Transcriptase Inhibitors (NtRTIs). Other inhibitors include delavirdine, efavirenz, rilpivirine, nevirapine, and nucleoside reverse transcriptase inhibitors (NRTIs), such as zalcitabine, lamivudine, azvudine, stavudine, and emtricitabine can also be used to show the antiviral activity against SARS-CoV-2. More Preclinical and clinical trials should be conducted to evaluate the clinical trial progress in silico trials, even though some have previously been evaluated by molecular docking. [50] As a result of interfering with the protein activity, ribavirin and sofosbuvir can be tightly bonded to the newly evolved RdRp coronavirus and eradicate the virus. It is important to note that sofosbuvir functions as a strong inhibitor of the recently discovered HCoV COVID-19 type.

#### 6.1. Neuraminidase Inhibitors

##### 6.1.1. Oseltamivir

A neuraminidase inhibitor is oseltamivir (Figure 7). [144] It is authorized for the prevention of influenza and the treatment of paediatric influenza. [205] Due to the unidentified presence of SARS-CoV-2 neuraminidase, drugs such as oseltamivir, peramivir, and zanamivir, which are neuraminidase inhibitors, are not anticipated to be effective in treating COVID-19 patients. [206] According to studies, people in Wuhan who have COVID-19 are treated with ganciclovir with oseltamivir or ritonavir/lopinavir with oseltamivir. Computational studies further supported the synergistic effects of ritonavir/lopinavir and oseltamivir in SARS-CoV-2. [207,208] Oseltamivir was utilised in Afghanistan along with ceftriaxone and terbutaline to treat COVID-19 patients. It is revealed that three days of oseltamivir therapy significantly improved the patients' lungs on the CT scan. In Singapore and Indonesia, oseltamivir is utilised as the COVID-19 treatment of choice. [50]

Oseltamivir is administered orally for the treatment of COVID-19 and suspected patients in Chinese hospitals, however, there is currently no solid proof that it has a tangible impact on the recovery of COVID-19 patients. [207]



**Figure 7.** Chemical structures of Neuraminidase inhibitors, such as Oseltamivir, Zanamivir, and Peramivir.

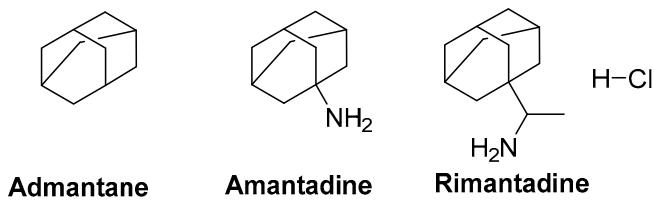
#### 6.1.2. Zanamivir and Peramivir

Another neuraminidase inhibitor that can be used for ventilated COVID-19 patients who are resistant to oseltamivir treatment is the zanamivir solution. Peramivir, as an antiviral medication, is given intravenously. Peramivir has a certain response for patients who do not respond to zanamivir or oseltamivir. [206,207] In Chinese hospitals, oseltamivir was administered orally to patients with 2019-nCoV confirmed infections. Oseltamivir may be helpful for treating COVID-19 patients, although there is currently no concrete evidence to support this. It has recently been suggested that neuraminidase inhibitors like oseltamivir, peramivir and zanamivir (Figure 7) are ineffective against COVID-19 and are not advised to be utilised for treatment procedures. [206]

#### 6.2. M2 Ion-Channel Protein Target

##### Adamantane, Amantadine, and Rimantadine

The pH of the viral sheath must be kept constant through the M2 channel protein on the sheath. The channel, in order for steward cells to enter and pass through the trans-Golgi membrane prior to viral maturation, is essential, as well as in combating influenza viruses. A previous study demonstrated that amantadine could inhibit the HCV p7 protein, which is crucial for producing ion channels in the host cell membranes. Amantadine (Figure 8) reportedly has a potent *in vitro* action against coronavirus, according to a 1973 publication. [208] A recent study demonstrated that amantadine (Figure 8) could inhibit SARS-CoV protein-membrane channel function. [209] Even though there is growing evidence that amantadine possesses antiviral potency appropriate for COVID-19 treatment, further investigation is necessary to determine its effectiveness. [50,210]

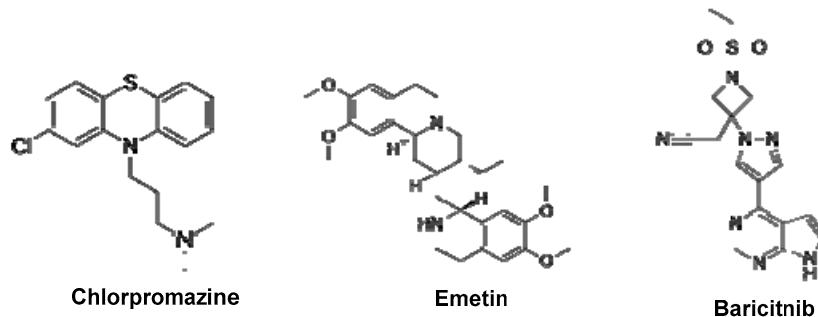


**Figure 8.** Chemical structures of M2 channel protein target such as Adamantane, Amantadine, and Rimantadine.

#### 6.3. Non-Antiviral Drugs against SARS-CoV-2

##### 6.3.1. Baricitinib

Baricitinib (Figure 9) has a high affinity against the Janus kinase (JAK) inhibitor by binding to and inhibiting adaptor-associated protein kinase 1 (AAK1). As a result, it may decrease both the inflammatory response and viral penetration brought on by SARS-CoV-2 infection. JAK inhibitors are used to treat rheumatoid arthritis and inflammatory diseases, including cancer. [211] Similar to baricitinib, JAK inhibitors such as ruxolitinib and fedratinib raise the degree of clathrin-mediated endocytosis, which may make them less efficient at lowering viral infectivity to tolerable levels. Lymphocytopenia, neutropenia, and viral reactivation are linked to its medical use. [50] Recent research has shown that the immunomodulatory drug Baricitinib and the antiviral Remdesivir have a good therapeutic effect against COVID-19. [212] By inhibiting JAK1/JAK2, baricitinib is anticipated to alleviate the cytokine storm brought on by COVID-19. Many clinical trials have been conducted worldwide, and one of them, in which baricitinib (2-4 mg) was universally provided for 1-2 weeks, showed encouraging results. Baricitinib should only be administered with extreme caution in patients with risk factors. For its use in pregnant women, human data is insufficient. [213] The patients with renal insufficiency should therefore be cautiously examined, along with termination or dose modification. [214]



**Figure 9.** Chemical structures of some non-antiviral drugs, Chlorpromazine, Emetin, Baricitinib targeting Importin  $\alpha/\beta 1$ -mediated nuclear import inhibitors.

#### 6.3.2. Ivermectin; Importin $\alpha/\beta 1$ -Mediated Nuclear Import Inhibitors

Ivermectin, is an anti-parasitic medication, approved by FDA. It has also been demonstrated to be an effective antiviral for both the Dengue virus and HIV in humans. [202,215] A single dose of the drug can reduce the viral RNA by around 5000 times. [216] The importin  $\alpha/\beta$  heterodimer pre-formed that delivers the viral protein charge nuclearly may also be isolated. [50] Ivermectin is seen as a potential therapeutic inhibitor against RNA viruses because it blocks the nuclear transport pathway of viral proteins, which is essential to the host's antiviral response. [216,217] Ivermectin has recently been shown to have the ability to reduce viral RNA to 5000 times after 48 hours of SARS-CoV-2 infection. [202] Research to establish the ideal dosage utilising the well-established safety profile for anti-parasitic therapy is part of demonstrating the efficacy of ivermectin in COVID-19 treatment. [45,218] Further investigation is necessary to determine its efficacy against COVID-19. Additionally, ivermectin has demonstrated a broad spectrum of antiviral activity. By preventing NS3 helicase activity, it directly prevents the yellow fever virus from replicating. [219] Moreover, it stops importin  $\alpha/\beta/1$ , which facilitates the passage of proteins between the nucleus and cytoplasm, which is necessary for HIV-1 replication and dengue viruses. [46,215,219] Recently, a case-controlled retrospective analysis suggested that ivermectin medication at a dose of 150 mcg/Kg might reduce the hospital admissions length and the mortality risk. Before ivermectin's efficacy can be verified in patients with SARS-CoV-2 infection, randomised controlled clinical trials are required. [50] For the treatment or prophylaxis of COVID-19, hydroxychloroquine and ivermectin combination medicine was recommended. Because of its dual effects on viral replication and viral assembly, this combination may have a synergistic effect. [220] Although the pharmacokinetic evaluation revealed that greater dosages were required to achieve antiviral activity, administering the prescribed inhibitory concentration in humans is likewise highly difficult. [221]

### 6.3.3. Interferon $\alpha$ and $\beta$

Interferons (IFNs), a broad-spectrum antiviral medication, are cytokines that activate the innate immune system in response to the viral infection. The antiviral activities and immunomodulatory of IFN can simulate protein production. IFN may also enhance the immune cells of the host cell's particular cytotoxic action. [221] Furthermore, the interferon (IFN) response is the first crucial one of protection against viruses. Type I and type III IFN responses against viral infections are stimulated by recognition of the innate immune sensing. [222] Many disorders, such as multiple sclerosis (MS) and viral hepatitis, have already been treated with pegylated and recombinant IFN  $\alpha/\beta$ . As a result, the IFN proposal against COVID-19 has demonstrated widespread concern. [210,223] Therefore, it is essential to thoroughly understand the biology of coronavirus infections to include rational therapeutic strategies and assess their clinical efficacy in COVID-19. [224] Although the cytokine development or robust chemokine or clinical investigations have revealed that the IFN reaction in patients is not mediated by significant IFN-I development. [216] When inflammatory chemokines and cytokines type I were analysed in the serum of COVID-19 patients, no substantial amounts were discovered, but pro-inflammatory chemokines and cytokines were found to be present in high levels. By tracking the transcriptome of SARS-CoV infected cells over time, other investigations shown that the IFN action on the virus can be delayed rather than completely eliminated. It was also shown that IFNs can inhibit the release of pro-inflammatory cytokines. [225] A systematic evaluation of 8 types of study, about 116 patients, found that using interferon in combination with ribavirin induced adverse side effects, including one patient who had evident hemolysis and two patients who had an increase in pancreatic enzymes. [226]

### 6.3.4. Teicoplanin

Teicoplanin, is an antibiotic glycopeptide frequently used to treat bacterial infections. Additionally, it is being utilised in treating SARS-CoV and is on prescription drugs lists for COVID-19. Teicoplanin is frequently used to treat viruses such as influenza, HIV, flavivirus, hepatitis C, ebola, and coronavirus; SARS-CoV and MERS-CoV. It can also cure gram-positive bacterial infections, particularly streptococcal and staphylococcal infections. [227] Teicoplanin inhibits the release of the viral genome and the viral replication cycle by cleaving the spike protein at low pH with cathepsin L; which enters the cell and targets the S protein in case of COVID-19, at the late endosomes during the early stages of viral replication. [228] The cathepsin L cleavage site has been preserved in the SARS-CoV and COVID-19 S proteins. The IC<sub>50</sub> for teicoplanin in vitro is 1.66 M, which is much lower than the amount of 8.78 M for a 400 mg daily dose in human blood. [206]

### 6.3.5. Emetine

Emetine, (Figure 9) a protein synthesis inhibitor, is used to treat amebiasis as an anti-protozoan; it also works to prevent malaria by interacting with the ribosomal E site on Plasmodium falciparum. Its therapeutic utility has recently been constrained due to potential cardiotoxicity. Many RNA and DNA viruses, such as Zika virus, Cytomegalovirus, Ebola virus, Buffalo poxvirus, HIV-1, Plague of the Tiny Ruminants virus, Echovirus-1, Newcastle virus, Herpesvirus Bovine 1, Herpes Simplex Virus-2, Metapneumovirus, Rift River Fever virus, and influenza viruses were tested for its antiviral effects. [229] Additionally, emetine was noted *in vitro* to suppress MHV-A59, SARS-CoV, and MERS-CoV. At 0.5 M, it was discovered to block the replication of SARS-CoV-2 effectively. In vitro, SARS-CoV-2 therapeutic plasma levels can approach 0.075 g/mL below EC<sub>50</sub>. The plasma has a toxic concentration of 0.5 g/mL. Remdesivir with 6.25 M combined with emetine with 0.195  $\mu$ m may decrease the viral generation by 64.9%; more *in vivo* studies are warranted. [202]

### 6.3.6. Chlorpromazine

The phenothiazine derivative chlorpromazine (CPZ), (Figure 9) which was chosen for Largactil, as the French brand name, has a wide range of properties, including antiviral, antifungal ones, anxiolytic, antiemetic, as well as immunomodulatory effects, the ability to modulate blood-brain

barrier function, the ability to inhibit clathrin-mediated endocytosis, and others. It works via chlorpromazine-HCl, preventing the modulator assembly on cell surfaces and endosomes, which stops the virus from entering host cells. In addition, chlorpromazine is used to treat schizophrenia and other psychotic illnesses, tetanus symptoms, nausea, acute intermittent porphyria, chronic hiccups, and anxiety. Recently, *in vitro* investigations found that the CPZ had anti-MERS-CoV and anti-SARS-CoV-1 action. Without an intensive care unit (ICU), it is thought that CPZ may reduce COVID-19 infection in patients who need respiratory support. [202,230]

#### 6.3.7. Aplidin

It was declared that aplidin had antiviral action, on March 2020. It is described that Multiple Myeloma is treated with aplidin on a large scale. The key to the virus's proliferation and spread is elongation factor 1 alpha (EF1A), which has been proven to be affected by aplidin *in vitro* tests. The antiviral activity of aplidin was initially investigated in human hepatoma cell line and HCoV-229E-GFP-related viruses. The early results are generally positive for SARS-CoV-2. [231]

#### 6.3.8. Rapamycin

Rapamycin was initially employed as an antifungal and later as an immunosuppressive medication for patients undergoing organ transplants. [232] It causes the signal transduction pathway to be interrupted downstream, which leads to the phosphorylation of mTOR. In some viral infections, such as H1N1 pneumonia, Andes virus, MERS-CoV, and HCV, mTOR inhibition prevents viral duplication and improves clinical outcomes. The well-known mechanism of action of the immunosuppressive drug rapamycin involves blocking mTOR kinase. A crucial part of viral replication is played by mTOR, and more especially by the protein complex mTORC1 that mTOR forms. It was demonstrated that rapamycin affected the PI3K/AKT/mTOR pathway, which prevented MERS infection. According to earlier research, rapamycin can regulate the production of virus particles, cytokine storms, and aid in the treatment of the illness. Consequently, it appears that rapamycin is an appealing choice for drug repurposing. Furthermore, compared to widely used antivirals, it might be a better option for COVID-19 therapy. Furthermore, the rapid mutation rate of viral RNA is unlikely to lessen its efficiency. [233–236]

#### 6.3.9. Lianhuaqingwen Capsule

In particular, lianhuaqingwen (LH) is utilised to treat influenza. [237] It reduces many symptoms such as muscle ache, headache, hyperpyrexia or fever, running nose, cough, aversion to colds, and nasal obstruction. The recommended dose is four capsules, three times a day. [129] LH was utilised by Chinese physicians to treat both mild and severe COVID-19 cases. As a potential treatment for SARS-CoV-2, LH has demonstrated effective anti-inflammatory and antiviral properties *in vitro* against coronaviruses. [238] Therefore, a different randomised controlled experiment (RCT) has shown that antiviral activity with LH can, in most cases, significantly relieve the COVID-19 symptoms, such as fever, fatigue, and cough. It may also significantly shorten and ease pneumonia symptoms without showing any noticeable negative effects. [239] Additionally, the antiviral potency of LH and other conventional Chinese medicines during a pandemic also effectively contributed to the treatment of SARS-CoV-2. [129]

#### 6.3.10. Convalescent Plasma

Convalescent plasma for COVID-19, also called "survivor's plasma," is blood plasma obtained from COVID-19-recovered patients. Recently, the FDA approved its use in hospitalised COVID-19 patients by issuing an Emergency Use Authorization. This demonstrated that COVID-19 plasma or clean monoclonal antibodies might be extracted from patients who have totally recovered and subsequently administered to another new patient for treatment. [240] Through Feb. 2020, about five COVID-19 patients in Shenzhen, China, received convalescent plasma treatment. Patients in this trial developed a specific anti-SARS-CoV-2 antibody 10 to 22 days after receiving convalescent plasma

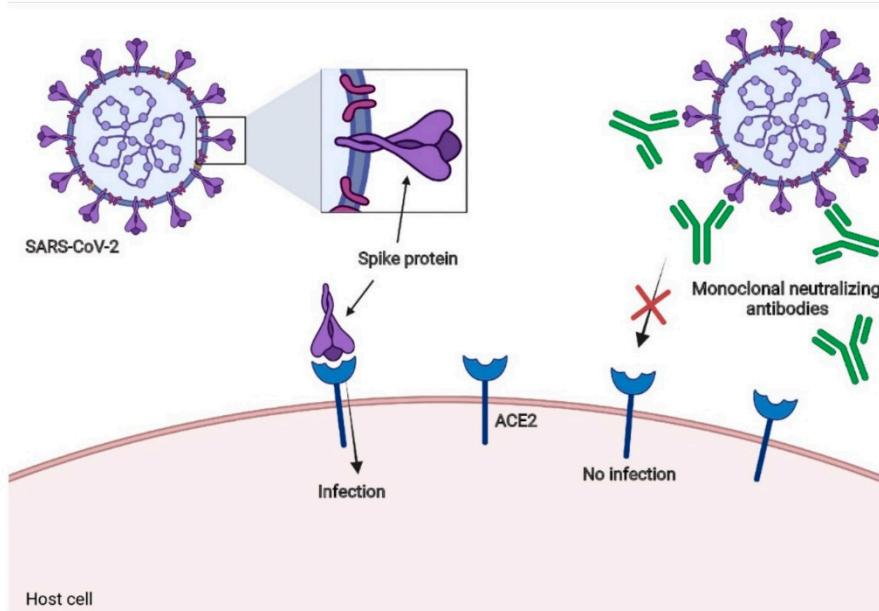
therapy. [241] Reduced viral loads and improved results in sequential organ failure were observed in four of the five patients. Their virus test was still negative after the transfusion for 12 days. After two weeks of admission, the four patients were taken off artificial ventilation. However, three individuals were discharged from the hospital after over 50 days. [242] Convalescent plasma therapy has positive results, despite the trial's extremely small sample size and then in the US, this approach of care is advised. [240]

### 6.3.11. Metformin

The hyperinflammatory state is a hallmark of COVID-19. Monocytes and macrophages are essential immune cells that metabolically reprogrammed when stimulated with different stimuli including SARS-CoV-2 spike protein. [243] Thus drugs which regulate immunometabolism could inhibit this inflammatory response. Pre-treatment of monocytes with metformin strongly suppressed spike protein-mediated metabolic reprogramming that also suppresses inflammatory responses to SARS-CoV-2. This has potential implications for the treatment of hyper-inflammation during COVID-19. [243]

## 7. Neutralizing Antibodies for SARS-CoV-2

Despite the fact that it has been effective in certain patients, convalescent plasma's potential is still debatable. In fact, allergic reactions, transmitted infections due to transfusion (ex. HCV, HBV, HIV), lung injury were observed in certain convalescent plasma trials. Furthermore, only a portion of plasma antibodies will be neutralizing; meanwhile the non-neutralizing antibodies will attach to non-spike protein antigens, compromising antibody responses and causing additional tissue damage. Moreover, convalescent plasma antibody titer is low and blood resources are limited. All of these drawbacks resulted in limiting the use of convalescent plasma treatment. Conversely, anti-SARS-CoV-2 monoclonal antibodies overcomes all the drawbacks of convalescent plasma by being able to specifically target the neutralizing sites and be manufactured in large quantities with ease of scalability. [244] Bamlanivimab, also known as LY-CoV555, was the first monoclonal antibody discovered to be effective against COVID-19 infection. LY-CoV555 exhibited potent binding and neutralizing action to ACE2 (Figure 10). Even at low doses, it could decrease the viral amount in respiratory tract samples. [245]



**Figure 10.** The mechanism of SARS-CoV-2 neutralizing antibodies. [246].

Another monoclonal antibody called etesevimab has always been utilized alongside with bamlanivimab. This combination has shown more efficiency than bamlanivimab monotherapy in reducing the viral load in outpatients with mild-to-moderate symptoms in addition to reducing the risk of hospitalization and death linked to COVID-19. [247,248] On February 9, 2021, they were approved for emergency use jointly due to their significant effectiveness in treating individuals with mild-to-moderate COVID-19. Yet, due to the Omicron variant's high frequency, the FDA has withdrawn the use of these monoclonal antibodies for COVID-19 treatment due to its ineffectiveness compared to Omicron variance. [248,249] However, the FDA and the National Institutes of Health have approved bebtelovimab, as the only effective neutralizing monoclonal antibody for the treatment of high-risk COVID-19 patients. [250] Additionally, Iketani et al. verified that, with the exception of bebtelovimab, three Omicron sub lineages demonstrated resistance to seventeen different neutralizing antibodies. [251,252]

## 8. Some Recently Synthesized Compounds and Approved for COVID-19 Treatment

### 8.1. Molnupiravir (MK-4482, EIDD-2801) (Ridgeback Biotherapeutics/MSD)

Molnupiravir, a prodrug antiviral medicine, Figure 11, was used to orally treat influenza A and B viruses, was just licenced in the United Kingdom and available in November 2021. It is a synthetic nucleoside N4-hydroxycytidine (NHC) derivative that inhibits specific RNA viruses by causing copying errors during RNA replication. Compared to its precursor NHC, this medication has a higher oral bioavailability in non-human primates and ferrets. It is also effectively digested in vivo after absorption, releasing the active compound into the plasma. Using in vitro studies, [253] NHC can prevent SARS-CoV-2 and other related coronaviruses. [254,255] The nucleoside analogue introduced by the viral RdRp during viral RNA synthesis leads to error catastrophe and suppression of RNA synthesis. [256] This property makes it a viable option for treating COVID-19. [257–259] Molnupiravir has demonstrated effectiveness in reducing viral loads and lung pathology in Syrian hamsters and human lung-only mice, whether administered before or after SARS-CoV-2 infection. [254,260] In ferrets, post-infection treatment with molnupiravir lowered virus levels in nasal lavages and impeded transmission to untreated contact animals. Moreover, hamsters infected with the B.1.1.7 (alpha variant) and B.1.351 (beta variant) of COVID-19 showed resistance to SARS-CoV-2 when treated with molnupiravir. A randomized, double-blind, placebo-controlled phase 1 trial with healthy volunteers revealed that oral doses ranging from 50 to 1600 mg of molnupiravir were well-tolerated, with only a few mild side effects reported. [261] Molnupiravir is being examined in phase 3 clinical trials for COVID-19 outpatient therapy (NCT04575584), postexposure prophylaxis (NCT04939428), and inpatient therapy (NCT04575597). According to MSD release and Ridgeback Biotherapeutics, [262] molnupiravir reduced the risk of hospitalisation or death in patients with mild-to-moderate COVID-19 disease around 50% compared to placebo and approved by the U.K.'s Medicines and Healthcare Products Regulatory Agency. [263]

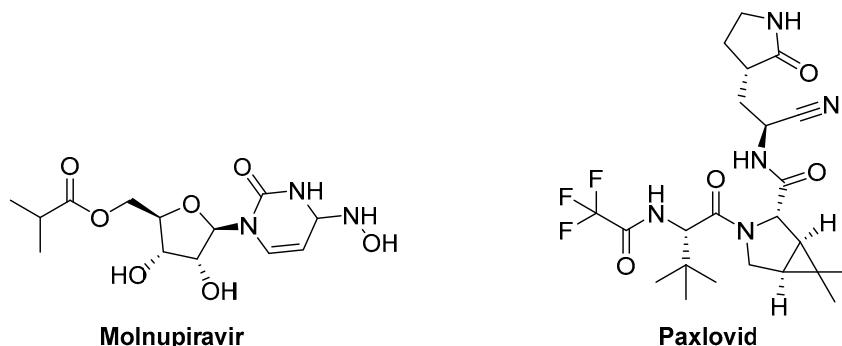


Figure 11. Chemical structures of Molnupiravir and Paxlovid.

### 8.2. Paxlovid (Pf-07321332)

Pfizer Inc. produced PF-07321332, an oral antiviral medication. It acts as an active 3CLpro protease inhibitor. The drug combination of PF-07321332/ritonavir for the COVID-19 treatment underwent phase III research and was marketed under the name Paxlovid. [167,168] As a combination, [264] ritonavir delays the cytochrome enzymes' metabolism of the PF-07321332, keeping larger levels of the primary medication in the blood. When taken within three days of the onset symptom, Pfizer's phase 2/3 results showed an 89% reduction in hospitals, it has been released in November 2021. [169,170] Ritonavir is coadministered in small doses to slow down PF-07321332 metabolism. [265]

## 9. COVID-19 and Cancer

It is commonly known that viral infections increase the likelihood of developing tumors. According to estimates, viruses are the primary cause of carcinogenic illnesses, which account for 15.4% of the cases of cancer. Numerous RNA viruses have been linked to increased cancer risk, and many can result in chronic infections. [266,267]

The majority of viruses use oncogenic processes that entail the continuous production of particular gene products that interact with cellular gene products to control proliferative or anti-apoptotic activity. For up to six months following a negative SARS-CoV-2 test, remnant SARS-CoV-2 nucleocapsid proteins were found in a number of extrapulmonary tissue samples, including those from the ileum, appendix, colon, lymph nodes and liver in individuals who had recovered with COVID-19. [268,269]

Additionally; it has been noted that acute COVID-19 infection patients have changed microbiota. This change was typified by an increase in opportunistic pathogens and a decrease in commensals, or beneficial bacteria, in the gut. [270]

Moreover, previous research has found that the tumor-suppressor proteins and SARS-CoV-2 spike overlap and that autoimmune cross-reactivity may be a possible mechanism behind future cancer recurrence after exposure to SARS-CoV-2.

In order to regulate p53, which poses a threat to SARS-CoV-2, it has evolved tactics similar to those of other viruses (such as the Epstein-Barr virus). Since the apoptotic signaling system depends heavily on the onco-suppressive protein p53, it has been suggested that long-term SARS-CoV-2 p53 suppression may have carcinogenic consequences. [267,271]

SARS-CoV-2-caused COVID-19 infection is deemed fatal since it has a wide-ranging impact on various organs, primarily the respiratory system. It damages the neurological, cardiovascular, and pulmonary systems, among other organs, leading to organ failure. Investigations should focus on how inflammation brought on by SARS-CoV-2 affects cancer cells and the environment around tumours. [272,273] The microenvironment tumour may change due to COVID-19, encouraging cancer cell growth and reawakening the dormant cancer cell (DCC). [274–276] When SARS-CoV-2 infection occurs, DCCs can reawaken and populate the pre-metastatic in the lungs and other organs, which can result in the spread of tumours. The most severe clinical effects of COVID-19 are DCC reawakening and subsequent neutrophil and monocyte/macrophage activation with an unregulated cascade of proinflammatory cytokines. The role of COVID-19 in inflammation, tumour growth, and tumour cell metastasis demand further investigation; the findings of these investigations will contribute to creating new targeted medicines for the treatment of COVID-19-positive patients as well as for the prevention of cancer. [277–279]

## 10. Conclusions and Public Health Perspectives

The WHO declared a pandemic on March 11, 2020, in response to the new coronavirus in the human, which sparked a global threat. It is undoubtedly one of the worst public health disasters two years later. Neither the SARS-CoV-2 development nor the severe and widespread effects of COVID-19 infections were anticipated. However, the quick reaction to the COVID-19 pandemic, and the responses taken by the WHO, governments, business, international researchers, and health authorities, has strengthened public health resilience and assisted in reducing adverse effects on society. These initiatives openly disclosed data on infection rates and fatalities in terms of clinical

trials. The severity of SARS-CoV-2 was lessened by open research, such as the early disclosure of the viral genome, patient trial validation of vaccine candidates, industry involvement in the development, and governments' speedy licensing of new diagnostic tests and vaccinations. Researchers and experts are determined to develop innovative therapeutic tactics quickly and plan to combat the terrible COVID-19 epidemic. Creating new vaccines and employing some FDA-approved medications that might be tested against COVID-19 and are viewed as repurposed drugs are two therapeutic approaches. The effectiveness of many classes of currently licensed and candidate vaccines and repurposed medications (such as interferons, non-antivirals and antivirals, and antiparasitic medicines), against COVID-19 infections have been reported. The effectiveness of several drugs has been presented and categorised according to their mechanisms of action against SARS-CoV-2. In-depth discussion was given in this study of antiviral medications, along with protease inhibitors, fusion inhibitors, M2 ion-channel protein blockers, neuraminidase inhibitors, neutralizing antibodies, and other non-antiviral drugs that may have effects against SARS-CoV-2. The recently FDA-approved drugs molnupiravir and PF-07321332 shed insight on their mode of action and eligibility as cutting-edge oral medications that fight SARS-CoV-2 by reducing hospitalizations for COVID-19 patients. Regarding the effectiveness of the vaccinations, it has been noted that Pfizer, Moderna, Fosun Pharma, BioNTech, and NIAID vaccines may be found to be the most effective to combat COVID-19. These vaccines are now being used, although they have significant drawbacks, including viral and host issues. As a result, choosing to get immunised with any of the licensed vaccinations must be done so under medical supervision and after taking the results of current clinical studies into account. Several lessons have been learned from the pandemic, including the urgency of large-scale vaccine production and distribution, the need for point-of-care diagnostic tests and, the importance of addressing the trade in wild animals and ecosystem destruction as significant contributors to the spread of infectious diseases. The COVID-19 pandemic's lessons such as the necessity of point-of-care diagnostic testing, the urgency of producing and distributing vaccines on a broad scale, and the significance of managing ecosystem devastation and trading in wild animals as major factors to the propagation of infectious illnesses; will be crucial for addressing future dangers to the public's health, particularly those brought on by new viruses or diseases.

**Authors Contribution:** R.F.B., A.V.S. and D.G. contributed equally to the conception and design of the study, as well as the analysis and interpretation of the data. They both played a significant role in drafting and revising the manuscript critically for important intellectual content. V.T. participated in the study's design, data analysis, and interpretation. She was also involved in drafting and revising the manuscript, providing important intellectual input. A.M.A. contributed to the acquisition of data, data analysis, and interpretation. He also played a role in drafting and revising the manuscript. K.A., M.M.E. was involved in the conception of the study and the acquisition of data. They provided critical input during the drafting and revision of the manuscript. All authors read and approved the manuscript.

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